

REMARKS

By this amendment, claims 27, 28, 35, and 38 have been amended, claims 63-64 have been added, and claims 29-34 and 39-40 have been cancelled without prejudice. The amendments to the claims are supported in all cases by the specification, e.g., at page 24, and no new matter has been added. Claims 41-62 stand withdrawn from consideration, and thus, claims 27-28, 35-38, and 63-64 are currently under examination in the present application. For the reasons set forth below, Applicants submit that the present amendments and arguments place this application in condition for immediate allowance.

As an initial matter, Applicants wish to thank the Examiner for granting the recent Interview with Applicants' counsel. By the present amendments, Applicants have now amended the claims of the present application in the manner suggested by the Examiner during the Interview of October 5, 2010, such that the claims are more clearly directed toward the elected combination of an antipsychotic or an antidepressant and an antagonist and/or inverse agonist of the histamine H₃ receptor, namely olanzapine and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether (BF2.649) or pharmaceutically-acceptable salts thereof. Furthermore, as discussed below and also in accordance with the Examiner's suggestions during the Interview, Applicants are hereby submitting a Declaration of Jean-Charles Schwartz pursuant to 37 C.F.R. §1.132 as further evidence of the unexpected and synergistic results which are achieved by the present invention and are reflected in the claims of the present application, as amended.

Before discussing those results, however, in the Office Action dated April 12, 2010, the Examiner maintained a provisional rejection of claims 27-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-28 of co-pending U.S. Application No. 11/815,736. In particular, the Examiner continued to assert that claims 25-28 of the co-pending application are directed to a composition comprised of 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether (hydrochloride salt) and that claims 27-33 of the present application are drawn to the same invention. Without further addressing the merits of the Examiner's assertions, Applicants are submitting herewith a terminal disclaimer pursuant to 37 C.F.R. 1.321 and, accordingly, Applicants thus respectfully submit that the Examiner's obviousness-type double patenting rejection should be withdrawn.

In the Office Action, the Examiner also maintained a rejection of claims 27-33 and 35-38 under 35 U.S.C. §103(a) as being unpatentable over International Patent Application Publication No. WO 00/74784 ("Todd") and U.S. Patent No. 7,138,416 ("Schwartz"). In particular, the Examiner continued to assert that, although neither Todd nor Schwartz teaches a specific combination of olanzapine and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, it would have been obvious to formulate a composition comprised of olanzapine and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether because Schwartz teaches that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether is effective in treating obesity and cognitive deficits, and because Todd teaches that compositions comprised of olanzapine and H₂ histamine antagonists are effective in reducing weight gain. Furthermore, the Examiner also commented that even though Todd teaches a

combination that includes an H₂ antagonist instead of an H₃ antagonist, such as 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, one of ordinary skill in the art would have been motivated to substitute the H₂ antagonist with an H₃ antagonist. For the reasons set forth below, Applicants submit that the Examiner's rejection is respectfully traversed and should be withdrawn.

Contrary to the Examiner's assertions, one of ordinary skill in the art would not have found it obvious to simply substitute H₂ antagonists with H₃ antagonists or inverse agonists as the Examiner has suggested for the treatment of weight gain, much less would one of ordinary skill in the art have made such a substitution based on the teachings of Todd, which is specifically directed toward H₂ antagonists. Todd is in fact purely speculative with regard to weight gain reduction and no experimental results are given. Moreover, effects opposite to those contemplated by Todd were actually reported in the literature following controlled double-blind clinical studies that showed that various H₂ antagonists (such as famotidine and nizatidine) in combination with olanzapine did not decrease the weight gain induced by olanzapine. *See, e.g.*, the attached article by Poyurovsky et al., *Eur Neuropsychopharmacol* 14(4), 332 (2004) (reporting the absence of weight gain reduction with famotidine); *see also* the attached article by Assuncao et al. 28(4), 270 (2006) (reporting the absence of weight gain reduction with nizatidine).

Furthermore, as set forth in the Declaration of Jean-Charles Schwartz submitted herewith pursuant to 37 C.F.R. §1.132, and as would also be recognized by those of ordinary skill in the art, H₂ antagonists and H₃ antagonists are completely distinct from one another and one of ordinary skill in the art would not have found it a simple matter to

substitute H₂ antagonists with H₃ antagonists for at least the following reasons (which are also discussed in the review by Schwartz et al Physiol Rev 71, 1-51 (1991) attached hereto):

a. H₂ and H₃ receptors are structurally distinct and their genomic structures share poor homology;

b. H₂ and H₃ receptors are present at distinct locations with H₃ receptors being exclusively located in the brain and H₂ receptors being essentially located out of the brain.

c. H₃ receptors are pre-synaptic whereas H₂ receptors are post-synaptic;

d. H₃ receptor antagonism leads to histamine release in the brain whereas H₂ receptor antagonism interferes with histamine actions;

e. H₃ receptors are associated with Gi proteins whereas H₂ receptors are associated with Gs proteins, Gi and Gs proteins having essentially opposite effects;

f. H₃ receptors inhibit the formation of cyclic AMP, whereas H₂ receptors activate the cyclic AMP formation; and

g. H₃ receptors are an electrophysiologically neuronal inhibitor whereas H₂ receptors are is a neuronal exciter.

In light of these differences in H₂ antagonists and H₃ antagonists, it is thus apparent that H₂ antagonists and H₃ antagonists have completely distinct modes of action and have the opposite effects on histamine. Indeed, H₂ antagonists are known to prevent the action of histamine and, in particular, are known to block the action of histamine in the stomach of individuals to thereby decrease gastric acid secretion. In contrast, H₃

antagonists reinforce the action of histamine by causing its release from cells and do so mostly in the brains of individuals, where H₃ receptors are primarily found. As such, and upon a review of Todd, it is thus necessarily the case that one of ordinary skill in the art would not have even contemplated that H₃ antagonists could be combined with an antipsychotic agent to achieve a desired reduction in weight gain. Instead, one of ordinary skill in the art would have used an H₂ antagonist to combat the weight gain caused by antipsychotic agents because Todd clearly and unambiguously teaches away from the inclusion of H₃ antagonists in an olanzapine-containing pharmaceutical composition by indicating that an H₂ antagonist, which has a different mode of action, should be used.

In the Office Action, the Examiner further asserted that it would have obvious to formulate a composition comprised of olanzapine and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether because Schwartz teaches that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether is effective in treating obesity and cognitive deficits, and because Schwartz also teaches that H₃ receptor antagonists may be used with psychiatric agents, such as neuroleptics, to increase the efficacy of those agents and to reduce their side effects. However, as pointed out in response to the previous Office Action in this case, Schwartz does not include any teaching or suggestion with respect to the particular side effects that may be countered by administering an H₃ antagonist in combination with an psychiatric agent, and certainly does not teach or suggest which of the side effects of olanzapine can be reduced by combining olanzapine with 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether. Indeed, given the fact that obesity is a multi-factorial disease,

Schwartz's mere reference to the use of H₃ antagonists in treating obesity simply cannot be regarded as a teaching or suggestion that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether could be combined with olanzapine and used to provide a pro-satiety effect and reduce olanzapine's undesirable side effect of weight gain. Accordingly, it is thus the case that neither Schwartz nor Todd include any teaching or suggestion with regard to a specific pharmaceutical composition that includes the olanzapine, as a specific antipsychotic or antidepressant agent, and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, as an antagonist or inverse agonist of the histamine H₃ receptor, much less any teaching or suggestions that such a combination could be used to reduce the undesirable side effects associated with olanzapine.

Furthermore, it is also the case that neither Todd nor Schwartz include any teaching or suggestion with regard to the unexpected, synergistic results that were achieved by combining olanzapine with 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether. As described in the attached Declaration of Jean-Charles Schwartz, and as set forth in Example 5 of the present application, Applicants unexpectedly discovered that when olanzapine and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether (BF2.649) were combined in a pharmaceutical composition, the composition provided synergistic effects that were not observed when either agent was administered individually. In particular, it was observed that when a group of volunteers was administered either a placebo, olanzapine alone (5 mg), BF2.649 alone (60 mg), or a combination of olanzapine (5 mg) and BF2.649 (60 mg) and were then evaluated on their levels of alertness, cognition, and satiety, it was found that olanzapine caused a decrease in alertness and cognition as well

as a marked increase in feelings of hunger. BF2.649 was found to have the opposite effect on those symptoms; however, when a combination of olanzapine and BF2.649 were administered, it was surprisingly found that the combination provided a synergistic effect beyond what was observed when BF2.649 was administered alone. In particular, it was observed that when olanzapine was combined with BF2.649 in the amounts indicated above, a total prevention of the effects of olanzapine on alertness, cognition, and satiety was observed. Such synergistic results are neither taught nor remotely suggested by the cited Todd and Schwartz references.

Similarly, and as shown in the results included in Appendix 1 of the attached declaration of Jean Charles Schwartz, the synergistic effects of combining olanzapine and BF2.649 were also apparent when the effects of that particular combination on feelings of hunger were analyzed and compared to the administration of a control and each separate ingredient alone. From those results, it was apparent that olanzapine greatly induced the hunger of feeling. However, it was further apparent that, when BF2.649 was co-administered, the induced feeling of hunger was totally inhibited and restored to control levels. That total inhibition of side effects induced by olanzapine thus further reflects the synergy exerted by the claimed combination, which again could not have been reasonably expected by the skilled person.

Finally, and in accordance with the new guidelines regarding “Developments in the Obviousness Inquiry after *KSR v. Teleflex*”, 75 Fed. Reg. 53, 643 (effective September 1, 2010), it is also noted that the obvious to try rationale invoked by the Examiner in the present Office Action simply cannot be applied in this case. As set forth

above, one of ordinary skill in the art would not have 1) any reason to substitute an H₂ antagonist with an H₃ antagonist, or 2) a reasonable expectation of success in view of Schwartz or Todd, alone or in combination. Although the Examiner has alleged that, in view of Schwartz, one of ordinary skill in the art would have substituted the H₂ antagonist of Todd with an H₃ antagonist, such an allegation is based on the assumption that H₂ antagonists and H₃ antagonists would even be substitutable with one another in the first place. However, it is noted that Todd only mentions the activity of H₂ antagonists without substantiating it with any experimental results, and thus, one of ordinary skill in the art would not have seriously contemplated the alleged speculative activity, much less have extended the alleged teaching to H₃ antagonists and done so with a reasonable expectation of success.

In summary, it is simply not the case that it would be obvious to one of ordinary skill in the art to simply replace an H₂ antagonist in a composition containing both an H₂ antagonist and olanzapine with an H₃ antagonist, much less would it be expected that such a substituted composition would achieve a desired reduction in the side effect of satiety caused by the olanzapine that is similar to what was purported to be achieved by combining an H₂ antagonist with olanzapine. To the contrary, as discussed above, the distinct effects of H₂ antagonists and H₃ antagonists are well known in the art, and it would not be expected that an H₂ antagonist could be substituted with an H₃ antagonist in a composition containing olanzapine and then used to provide the synergistic results discussed above.

Accordingly, in light of the foregoing discussion, Applicants submit that the present invention is not rendered obvious by the cited references and that the claims of the present application are clearly patentable over those references. Applicants thus submit that the Examiner's rejections on the basis of those references is respectfully traversed and should be withdrawn.

In light of the amendments and arguments provided herewith, Applicants submit that the present application overcomes all prior rejections and objections and has been placed in condition for immediate allowance. Such action is respectfully requested.

Respectfully submitted,

Date: January 12, 2011



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IN THE U.S. PATENT AND TRADEMARK OFFICE

U.S. Appl. No.: 10/562,396 Confirmation No.: 8440
Title: COMBINATION PRODUCT COMPRISING AN ANTAGONIST
OR INVERSE AGONIST OF HISTAMINE RECEPTOR H₃ AND
AN ANTIPSYCHOTIC AND ANTIDEPRESSANT AGENT, AND
USE THEREOF FOR THE PREPARATION OF A
MEDICAMENT THAT PREVENTS THE ADVERSE EFFECTS
OF PSYCHOTROPIC DRUGS
Inventor(s): Jean-Charles Schwartz, et al.
Filed: April 14, 2006
Art Unit: 1627
Examiner: Pihonak, Sarah
Docket No.: P08824US00/BAS
Customer No.: 000881

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DECLARATION OF JEAN-CHARLES SCHWARTZ
PURSUANT TO 37 C.F.R. §1.132

Sir:

I, Jean-Charles Schwartz declare and state as follows:

1. I am a French citizen and I am an honorary Professor and Chairman at Université René Descartes in Paris, an honorary member of the Institut Universitaire de France, a member of the European Academy (Academia Europea), a member of the French Academy of Sciences. I have also authored over 700 publications in international journals.

2. I am a co-inventor and am familiar with the subject matter described and claimed in the above-identified patent application. The present patent application is directed to a pharmaceutical composition that includes a combination of olanzapine, as an antipsychotic or antidepressant agent, and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether ("BF 2.649"), as an antagonist and/or inverse agonist B of the histamine H₃ receptor. The composition is capable of suppressing or limiting the increased weight gain, decreased alertness, and decreased cognitive effects that are normally observed during treatment with olanzapine.

3. I have also reviewed the Office Action that was mailed April 12, 2010 and the references cited therein. My understanding is that in conjunction with this application, the Examiner has made the assertion that it would be obvious to one of ordinary skill in the art to simply replace an H₂ antagonist, in a composition containing both an H₂ antagonist and olanzapine, with an H₃ antagonist, and that it would be expected that such a substituted composition would achieve a desired reduction in the side effect of weight gain caused by the olanzapine that is similar to what was purported to be achieved by combining an H₂ antagonist and olanzapine. For reasons as stated below, such is not the case.

4. As an initial matter, the skilled person would have not seriously conceived in view of Todd et al. (WO 00/74784) that H₂ antagonists in combination with olanzapine would decrease weight gain caused by olanzapine. First, Todd et al is in fact purely speculative with regard to weight gain reduction and no experimental result is given. Second, opposite effects were reported in the literature following controlled double-blind clinical studies that showed that various H₂ antagonists (such as famotidine and nizatidine) in combination with olanzapine did not decrease the weight gain induced by olanzapine. For example, see in this respect the attached Poyurovsky et al Eur Neuropsychopharmacol 14(4), 332 (2004) reporting the absence of weight gain reduction with famotidine, and Assuncao et al 28(4), 270 (2006) reporting the absence of weight gain reduction with nizatidine.

5. Moreover, the skilled person considering the teaching of Todd et al, would understand it is not a simple matter to substitute an H₂ antagonist with an H₃ antagonist and/or inverse agonist for at least the following reasons:

a. H₂ and H₃ receptors are structurally distinct: their genomic structures share poor homology;

b. H₂ and H₃ receptors locations are distinct: H₃ receptors are exclusively located in the brain whereas H₂ receptors are essentially located out of the brain. Further, H₃ receptors are pre-synaptic whereas H₂ receptors are post-synaptic;

c. H₃ receptor antagonism leads to histamine release in the brain whereas H₂ receptors antagonism interferes with histamine actions;

d. H_3 receptor is associated with Gi proteins whereas H_2 receptor is associated with Gs proteins, Gi and Gs proteins having essentially opposite effects;

e. H_3 receptor inhibits the formation of cyclic AMP, whereas H_2 receptor activates the cyclic AMP formation; and

f. H_3 receptor is an electrophysiologically neuronal inhibitor whereas H_2 receptor is a neuronal exciter.

These features are reported in the review Schwartz et al Physiol Rev 71, 1-51 (1991), attached hereto.

6. It therefore appears from the above that H_2 receptors antagonists and H_3 antagonists have completely distinct modes of action and have the opposite effects on histamine. H_2 antagonists are known in the art as agents that inhibit the action of histamine and, in particular, are known to block the action of histamine in the stomach of individuals to thereby decrease gastric acid secretion. In contrast, H_3 antagonists reinforce the action of histamine by causing its release from cells, and do so mostly in the brains of individuals, where H_3 receptors are primarily found. As such, one of ordinary skill in the art, knowing this distinction between H_2 antagonists and H_3 antagonists, would not have reasonably considered that a purported effect of combining H_2 antagonists with olanzapine to prevent weight gain could also be obtained with a combination of H_3 antagonists and olanzapine.

7. In addition, it was unexpectedly discovered that when olanzapine and BF2.649 were combined in a composition, the composition provided synergistic effects that were not observed when either agent was administered individually. In particular, when a group of volunteers was administered either a placebo, olanzapine (5 mg) alone, BF2.649 (60 mg) alone, or a combination of olanzapine (5 mg) and BF2.649 (60 mg) and were evaluated on their levels of alertness, cognition, and satiety, it was observed that olanzapine caused a marked decrease in alertness and cognition, as well as a marked increase in feelings of hunger. BF2.649 was found to have the opposite effect on these various symptoms.

8. However, when a combination of olanzapine and BF2.649 were administered in the amounts indicated above, it was surprisingly found that the combination provided a total prevention of the side-effects of olanzapine on alertness, cognition, and satiety.

9. More particularly, results attached herewith as Appendix 1 show the effect on the hunger feeling for the particular combination of BF2.649 with olanzapine compared with control and each separate ingredient administered alone. It appears that:

- olanzapine greatly induces the hunger of feeling; and
- when BF2.649 is administered this induced feeling of hunger is totally inhibited

and restored to control levels.

This total inhibition of side effects induced by olanzapine reflects the synergy exerted by the combination. This synergy could not have been reasonably expected by the skilled person.

10. Accordingly, as indicated above, the references cited by the Examiner are also distinguishable from the present claims. For example, Todd et al. (WO 00/74784) is in fact purely speculative with regard to weight gain reduction, and does not provide any data supporting this mere allegation. Further, Todd et al. is specifically directed to H₂ antagonists. H₂ antagonists and H₃ antagonists have completely distinct modes of action. More specifically, H₂ antagonists and H₃ antagonists have opposite effects on histamine: H₂ antagonists prevent the action of histamine, whereas H₃ antagonists reinforce the histamine action. More particularly, H₃ antagonists release histamine in brain: this specific property leads to the prevention of anti-satiety effect of antipsychotic. This histamine release capacity is not shared at all by the H₂ antagonists. The skilled person, knowing this distinction between H₂ antagonists and H₃ antagonists would not have reasonably considered that the speculative effect of combining H₂ antagonists with an antipsychotic to prevent weight gain would possibly have been obtained with a combination of H₃ antagonists and said antipsychotic. This is in fact the opposite that could have been expected: in view of the opposite effect on histamine, the skilled person would have reasonably considered that the effect suggested in Todd et al. would not have been obtained with H₃ antagonist.

11. In addition, the Schwartz reference is cited by the Examiner with regard to the treatment of obesity. However, given the fact that obesity is a multi-factorial disease, mere reference to the use of H₃ antagonists in treating obesity simply cannot be regarded as a teaching or suggestion that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether could be combined with olanzapine and used to provide a pro-satiety effect.

12. Accordingly, the Examiner's assertion that it would be obvious to one of ordinary skill in the art to simply replace an H₂ antagonist in a composition containing both an H₂ antagonist and olanzapine with an H₃ antagonist, and that it would be expected that such a substituted composition would achieve a desired reduction in the side effect on satiety caused by the olanzapine that is similar to what was purported to be achieved by combining an H₂ antagonist with olanzapine, is simply not true. To the contrary, as discussed above, the distinct effects of H₂ antagonists and H₃ antagonists are well known in the art, and it would not be expected that an H₂ antagonist could be substituted with an H₃ antagonist in a composition containing olanzapine and then used to provide the synergistic results discussed above.

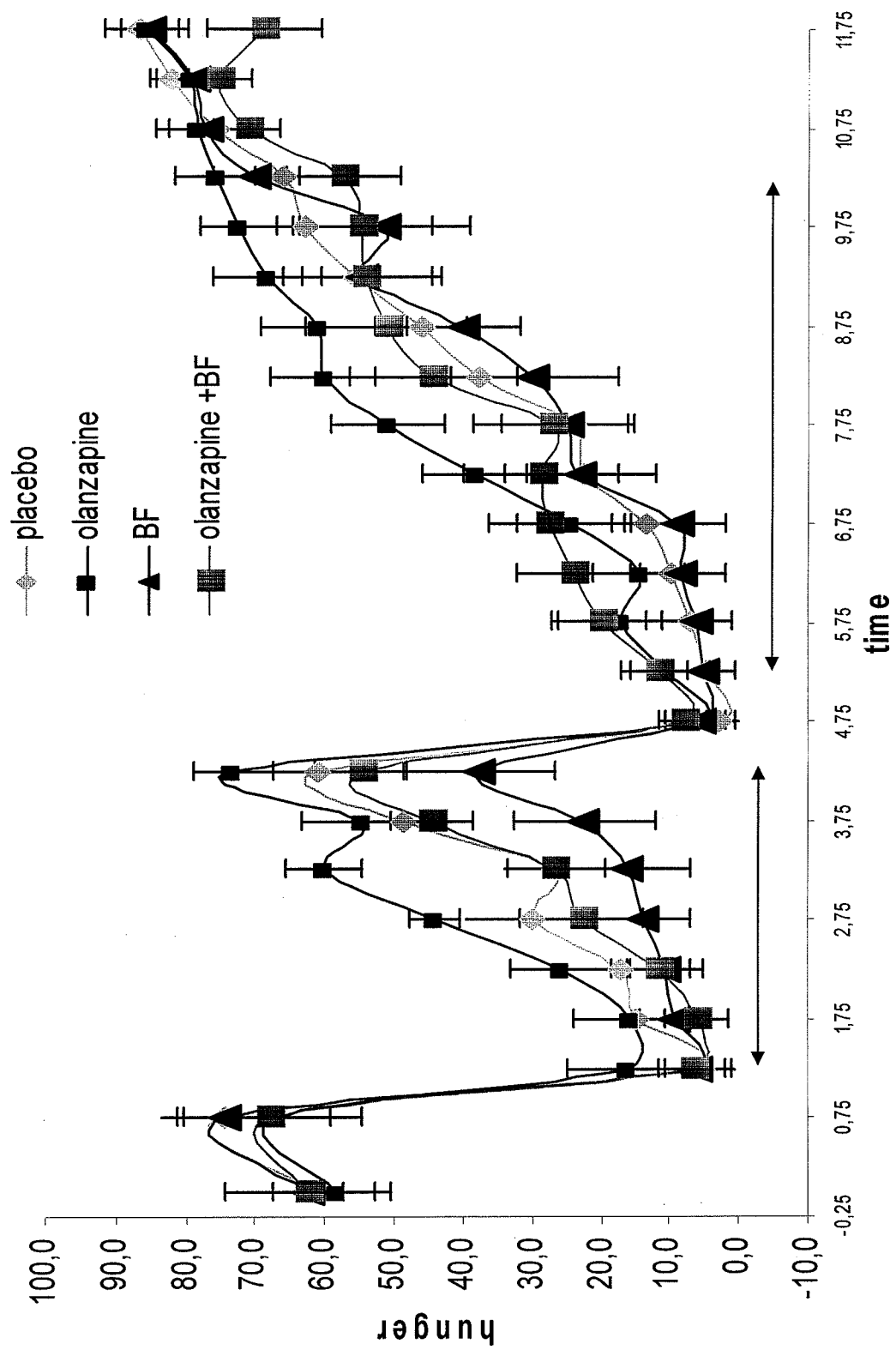
I hereby state that all statements made herein based on my own personal knowledge are true and correct and that all statements based on my information and belief are true and correct to the best of my knowledge, and further that all of these statements have been made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18

of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

4 Oct 2010
Date



Jean-Charles Schwartz



APPENDIX I

Physiological Reviews

Published and Copyright by
The American Physiological Society

Vol. 71, No. 1, January 1991

Histaminergic Transmission in the Mammalian Brain

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I. Introduction	2
II. Metabolism of Histamine	2
A. Biosynthesis	2
B. Storage	4
C. Release	5
D. Inactivation	6
E. Turnover	7
III. Disposition of Histaminergic Neuronal Pathways	8
A. Lesion studies	8
B. Immunohistochemical tools	9
C. Localization of histaminergic perikarya: tuberomammillary nucleus	9
D. Morphology of histaminergic neurons	10
E. Other putative transmitters in histaminergic neurons	11
F. Pathways and projection fields of histaminergic neurons	11
G. Ontogeny of histaminergic neurons	12
H. Afferents to histaminergic neurons	13
IV. Nonneuronal Stores of Histamine in Brain	13
A. Mast cells in brain	13
B. Other nonneuronal stores	14
V. Histamine Receptors in Brain	14
A. Histamine H ₁ receptors	14
B. Histamine H ₂ receptors	18
C. Histamine H ₃ receptors	20
VI. Role of Histaminergic Neurons in Neuroendocrine Controls	22
A. Posterior pituitary hormone secretion	22
B. Prolactin secretion	23
C. Thyrotropin secretion	24
D. Growth hormone secretion	24
E. Adrenocorticotrophic hormone secretion	24
F. Gonadotropin secretion	25
VII. Role of Histaminergic Neurons in Cardiovascular Regulation	25
VIII. Role of Histaminergic Neurons in Control of Cerebral Circulation	26
IX. Role of Histaminergic Neurons in Thermoregulation	26
X. Role of Histaminergic Neurons in Emesis and Motion Sickness	27
XI. Role of Histaminergic Neurons in Control of Nociceptive Responses	27
XII. Role of Histaminergic Neurons in Control of Vigilance, Sleep, and Wakefulness	27
XIII. Role of Histaminergic Neurons in Control of Various Behaviors	29
A. Stress	29
B. Motor activity	29
C. Drinking and eating	29
D. Aggressive behaviors	29
E. Self-stimulation, reinforcement, and aversion	29
F. Learning	30
G. Discriminative properties of H ₁ antagonists	30
H. Hallucinatory properties of H ₂ antagonists	30
XIV. Conclusion	30

I. INTRODUCTION

The recognition of histamine (HA) [or 2-(4-imidazolyl)ethylamine] as a messenger molecule in cell-to-cell communication began early in this century. The early history of HA was dominated by Sir Henry Dale, the great British pharmacologist; Barger and Dale (44) were the first to identify the amine in ergot extracts. Thereafter Dale and Laidlaw (151, 152) described the major actions of HA on tissues, i.e., its potent contractile effects on smooth muscles and the capillary dilative action. Popielski (579) described the only other important HA effect, the stimulant effect on gastric secretion.

In 1927, Dale and co-workers (68) were among the first to isolate HA from a variety of fresh tissues, thus establishing that HA is a normal constituent of the body. In fact its name derives from "histos," the Greek word for tissue. However, Dale was reluctant to accept the notion that endogenous HA could function as a messenger molecule, that is, that HA could be released from its tissue stores to affect the activity of target cells. It was Feldberg (211, 212) who clearly demonstrated that HA was released from the lung during the anaphylactic response and that it induced a marked bronchoconstriction.

These experiments suggested the role of HA in the mast cells of connective tissue, which are only one of its major stores. Although HA has long been suspected of not being restricted to mast cells, there was little knowledge of the localization and functions of the non-mast cells stores of the amine until recently.

Insights on possible HA functions in the central nervous system (CNS) have been much slower in arriving than studies on other amines. Nevertheless, the presence of HA in brain can be traced back as far as other biogenic amines (1). Kwiatkowski (426) found that HA was more concentrated in gray matter than in white matter, and White (817) first showed that local synthesis of the amine occurs in the brain.

It was not until 1970 that interest in brain HA resumed when sensitive radioisotopic assays for the amine and for L-histidine decarboxylase (HDC), its synthesizing enzyme, were developed (667, 743). These assays enabled the rapid accumulation of data, mainly biochemical, that indicated that HA needed to be added to the already long list of neurotransmitters. In particular, lesion studies performed by Garbarg et al. (232) demonstrated for the first time the existence of histaminergic neurons in mammalian brain. This was confirmed when immunohistochemical tools to detect the amine (552, 707, 821) or its synthesizing enzyme (802) became available, and the origin and projections of these neurons are fairly well established now. Meanwhile it had been established that cerebral HA could be released by depolarization and in a calcium-dependent manner (32) and that its turnover is rapid and can be modified almost instantaneously (568, 569).

Equally important in establishing the role of HA as a neurotransmitter was the demonstration of the presence in brain of three subclasses of receptors by bio-

chemical (25, 56, 618) and electrophysiological approaches (281).

Thus the two last decades of research have resulted in a coherent picture of the involvement of HA in neuronal communication. In addition, the design of an increasing number of pharmacological tools to selectively modify HA transmission and their utilization in electrophysiological, neurochemical, behavioral, and neuroendocrinological studies has led to a progressively more precise hypothesis about the functions of HA neurons in the CNS.

The topic of HA in mammalian brain has been the subject of various general reviews in the last few years (228, 277, 328, 577, 584, 615, 666). Specific HA neurons and their targets have also been identified in the CNS of the invertebrate mollusk *Aplysia*, but this topic is not considered here (for review see Ref. 811). The topics of brain HA receptors (105, 137a, 227, 255, 256, 304, 334, 659) and of methodology in brain HA research have also been reviewed (238, 786, 805).

II. METABOLISM OF HISTAMINE

A. Biosynthesis

Histamine poorly penetrates the brain from blood (648, 671) and therefore must be formed locally. Indeed, in vivo formation of radioactive histamine in brain was detected after administration of its radioactive precursor L-histidine (His) in cats (818), rats (571), or mice (789). Histamine biosynthesis involves two steps, i.e., transport of His into the cell and its decarboxylation by HDC (for reviews see Refs. 33, 238, 576, 805).

1. Histidine transport

Saturable, energy-dependent His uptake occurs in brain slices (788) and synaptosomes (127, 299, 365). The transport system in synaptosomes seems partly independent of Na⁺ and K⁺, and kinetic analyses revealed the presence of both high- and low-affinity components. L-Histidine uptake is stimulated by depolarization (299, 788). There is not yet evidence for the presence of a specific His transport system in HA neurons, since amino acid transport is not altered after lesions of the latter (299). However, detection of such a system might be difficult in view of the small number of HA nerve endings in brain. The His level is similar in the C₂ histaminergic and nonhistaminergic neurons of *Aplysia* (813).

2. Properties of L-histidine decarboxylase

L-Histidine decarboxylase (EC 4.1.1.22) and not dopa decarboxylase (EC 4.1.1.28) is responsible for the one-step HA formation in brain (42, 650, 651, 667, 745, 813). L-Histidine decarboxylase has been exclusively purified from various peripheral tissues displaying high

catalytic activity (268, 292, 454, 575, 576, 642, 643, 731, 758, 801, 806, 832) and from most studies appears as a protein of 110-125 kDa constituted of two identical subunits of 55-60 kDa with an isoelectric point around 5.5. The existence of various HDC isoenzymes has been suggested from isoelectric focusing patterns (454, 642, 643) and immunologic studies (804, 805). In addition, variation in the structure of kidney HDC in mouse strains affecting its affinity for its cofactor and its heat stability was shown and attributed to the existence of alleles of a single structural gene on chromosome 2 (455).

However, HDC from various rat tissues, including the brain, displays similar catalytic activity and is similarly recognized by both monoclonal (573-575) and polyclonal antibodies (731). Also HDCs in brain homogenates from *Aplysia californica* (813), rat (667), mouse (745), guinea pig (650, 651), rabbit (516), hamster (296), and human (42) display rather similar catalytic activity. Similar to other mammalian decarboxylases, HDC functions with the cofactor pyridoxal-5'-phosphate, which is so highly bound to the apoenzyme (456, 540, 541) that its addition to cerebral extracts does not result in marked increases in catalytic activity (Schwartz, Garbarg, and Pollard, unpublished observations). Characteristically, HDC decarboxylates His with a Michaelis constant (K_m) and a maximum rate (V_{max}) that change with the pH and ionic strength of the medium (33, 290, 667, 805). At a pH of ~ 7.0 in standard buffers the K_m of His is ~ 0.1 mM, a value that appears to be close to the plasma concentration and, presumably, the intraneuronal concentration of the amino acid, accounting for the observations that HA levels in rodent brain are increased after systemic administration of His in large dosages (668, 745). The turnover number of purified HDC (~ 0.4 s $^{-1}$) seems low compared with that of other amino acid decarboxylases (454).

Recently, the complete amino acid sequence of rat HDC was deduced from the cloning, from a fetal liver library, of a cDNA encoding the enzyme (367a). It comprises 655 amino acid residues, corresponding to a protein of 73 kDa, a value significantly higher than the 55- to 60-kDa values found after purification of the subunits, suggesting that HDC might be posttranslationally processed. Rat HDC displays distinct homologies with other pyridoxal phosphate-dependent enzymes, such as dopa decarboxylase, particularly in the region surrounding the putative cofactor-binding lysine residue (Lys³⁰⁷). The sequence comprises two consensus phosphorylation sites of cAMP-dependent protein kinase. The HDC gene was located to mouse chromosome 2, where it is closely linked to the β_2 -microglobulin gene (367a).

L-Histidine decarboxylase displays a high substrate specificity toward His, with the sole other decarboxylated natural amino acid being 3-methylhistidine, which yields *tele*-methylhistamine (*t*-MeHA) (674), a substance with little biological activity that is mainly formed in brain by methylation of HA. Because both the affinity of 3-methylhistidine for HDC and its tissue levels are low, the functional significance of this minor pathway remains doubtful. Other natural amino acids

display even lower apparent affinities for HDC, and their decarboxylation was not demonstrated (633). The two HDC inhibitors α -methylhistidine (194, 650) and α -fluoromethylhistidine (412) are decarboxylated by HDC.

In several peripheral tissues, such as the stomach or skin, HDC activity can be rapidly and markedly increased as a result of various treatments, e.g., by hormones (647), that may induce synthesis of HDC molecules (673). In brain, similar changes were not reported but, after its nearly total inactivation by a "suicide-inhibitor," cerebral HDC is synthesized at a high rate: $\sim 50\%$ of the initial HDC activity is recovered within 26 h in the hypothalamus, where HA perikarya are located, and within 58 h in the cerebral cortex, which contains nerve endings (235). From this time lag it has been inferred that HDC is transported at a rate of ~ 1 mm/h, roughly corresponding to the mean transport rate of other monoamine-synthesizing enzymes.

3. Localization of L-histidine decarboxylase

Biochemical and immunohistochemical studies have revealed the presence of HDC in the cytoplasm of a population of cerebral neurons (see sect. III). L-Histidine decarboxylase activity is distributed in a markedly heterogeneous fashion between cerebral regions, with the highest levels being found in hypothalamus, the lowest levels in cerebellum, and intermediate levels in telencephalic areas (55, 664, 667, 745). Heterogeneous distributions are also found among nuclei of the hypothalamus (567), upper brain stem (572), amygdaloid complex (60), or areas of the hippocampal formation (40). In contrast, HDC activity does not vary markedly between areas of the cerebral cortex (42, 231). These regional distributions of HDC activity are generally consistent with data derived from immunohistochemical studies (see sect. III).

Subcellular fractionation studies indicate that HDC is mainly found in the cytoplasm of isolated nerve endings (55, 745, 751), a conclusion confirmed by immunohistochemical studies at the electron-microscopic level (294). In the hypothalamus, which contains HA perikarya, a lesser proportion of HDC activity than in other areas is associated with subcellular fractions enriched in nerve endings (55), and HDC immunoreactivity is detected all over the cytoplasm surrounding the large cell nucleus of these neurons (294). In the neonatal brain, i.e., before formation of most HA synapses, HDC activity is low, particularly in telencephalic areas, and mainly recovered in soluble (nonsynaptosomal) subcellular fractions (457, 751). The earliest detection of HDC in hypothalamus during postnatal development is consistent with the expression of the enzyme in perikarya from this region (457).

Although HA neurons constitute the major localization of HDC, small fractions of the cerebral enzyme are held in mast cells (457).

4. Inhibition of L-histidine decarboxylase

Because HA is synthesized in a single step and by a highly specific enzyme, HDC inhibitors are potentially

useful tools with which to investigate the role of HA. Until recently, only compounds with limited specificity and low potency, such as α -hydrazinohistidine, brocresine, or α -methylhistidine, were available (433, 667, 668, 743, 745). In 1978, Kollonitsch et al. (412) designed *S*- α -fluoromethylhistidine (α -FMH) among a series of potential "suicide" or catalytic constant (K_{cat}) inhibitors of amino acid decarboxylases. *S*- α -fluoromethylhistidine potently inhibits in a stereoselective, time-dependent, concentration-dependent, and irreversible manner cerebral HDC with an inhibitor constant (K_i) of $\sim 10^{-5}$ M, whereas related decarboxylases such as dopa or glutamate decarboxylase are not significantly affected (235). Indeed α -FMH is a suicide substrate that remains bound to the enzyme after being decarboxylated (194, 421). *S*- α -fluoromethylhistidine is similarly potent on HDCs of humans (763), *Aplysia* (812), and even *Morganella morganii* (295).

From this mechanism it seemed feasible to covalently label and detect HDC autoradiographically on tissue sections; however, because of a high background, this procedure could not be applied to histochemistry (665). *S*- α -fluoromethylhistidine, administered systemically in rather low dosages, rapidly, completely, and in a long-lasting manner inactivates HDC in brain and peripheral organs (82, 83, 235, 296, 446, 692, 792). Restoration of activity occurs progressively, presumably as a result of neosynthesis of HDC molecules, and in brain the process is first detected in the hypothalamus in which HA perikarya are located (235). Because α -FMH efficiently depletes HA stores in cerebral neurons (235, 446), the drug is a useful tool for investigating the amine turnover and functions therein.

5. Regulation of histamine biosynthesis

Various treatments that drastically affect HA turnover in brain fail to alter its steady-state level to any large extent, implying the existence of efficient regulatory processes (356, 357, 360, 504, 571). The latter can even be demonstrated to occur in vitro, since the depolarization-induced release of [3 H]HA from slices or synaptosomes incubated in the presence of [3 H]His is accompanied by a large increase in the rate of [3 H]HA formation (23, 26, 28, 787, 788). In the absence of Ca^{2+} in the external medium, not only release but also stimulation of synthesis is abolished, suggesting some relationships between the two effects. However, this interpretation is not entirely clear, since [3 H]HA synthesis is already activated by removal of external Ca^{2+} in the absence of depolarization (28).

The mechanism by which external Ca^{2+} regulates [3 H]HA synthesis is not known, but parallel changes in catecholamine formation have been ascribed to activation of the rate-limiting enzyme tyrosine hydroxylase by phosphorylation via adenosine 3',5'-cyclic monophosphate (cAMP)- or Ca^{2+} -dependent protein kinases (252). A similar process was preliminarily suggested to occur in the case of cerebral HDC, the activity of which was enhanced by preincubation with a cAMP-dependent

protein kinase (191), but this could not be confirmed on mastocytoma HDC (291). Theoretically, depolarization-induced stimulation of [3 H]HA formation could result from an enhancement of [3 H]His uptake, but the latter is only weakly enhanced in slices (788) and even decreased in synaptosomes (127, 299). However, stimulation of a quantitatively minor but specific system for the amino acid uptake in HA neurons having so far escaped detection cannot be discarded. A direct feedback inhibition of soluble HDC by added HA has been excluded (668).

Histamine formation in brain slices and synaptosomes as well as in rat brain in vivo is, similar to [3 H]HA release, regulated via H_3 autoreceptors (23, 26, 28, 239). In vitro, K^+ -induced stimulation of [3 H]HA formation is reduced by 60-70% in the presence of HA or H_3 -receptor agonists in low concentrations; conversely, it is enhanced by H_3 -receptor antagonists, presumably via blockade of autoinhibition elicited by released HA, acting at the autoreceptors. The mechanism of H_3 receptor-mediated regulation of [3 H]HA formation is not known, mainly because the transduction system of H_3 receptors is not yet identified.

Stimulation of presynaptic M_1 muscarinic (270) or α_2 -adrenergic receptors (271) in slices or in rat brain in vivo also reduces [3 H]HA formation to the same extent as H_3 receptor stimulation does.

B. Storage

Histamine is present in the brain of invertebrates (607), lower vertebrates (10), and mammals. In several mammalian species, such as dogs (4), cats (5), rabbits (2, 254), monkeys (513, 741), guinea pigs (79), rats (619, 743), mice (629, 660), hamsters (296), and humans (440), it is distributed in a highly nonuniform manner between grossly dissected regions and even among nuclei in regions such as the hypothalamus (98, 567).

A variety of biochemical and pharmacological approaches strongly indicated that the cerebral amine was held in at least two classes of cellular stores, neurons and mast cells (654). With the advent of histochemical methods, these two classes of HA-storing cells have now been visualized (see sects. III and IV). Although mast cells are scarce in the brain, because of their high HA content they significantly contribute to the overall amine content, particularly in certain brain regions.

Data from subcellular fractionation studies (113, 231, 383, 423, 457, 467, 654, 697) are consistent with this dual localization. In mast cells from various tissues, HA is held in large granules that sediment with the crude nuclear (P_1) fraction. Consistently a fraction of cerebral HA ($\sim 20\%$) sediments with this fraction, a feature that is not observed for other amines. In addition, a larger fraction of the amine sediments with both the crude mitochondrial (P_2) and microsomal (P_3) fractions that both contain synaptosomes, i.e., pinched-off nerve endings. Within the P_2 and P_3 fractions, HA is largely bound to vesicles, whereas HDC is mainly soluble: this indicates that HA, similar to other neurotransmitters, is synthesized in the cytoplasm of nerve endings and

thereafter bound to synaptic vesicles. In the bovine retina, ~80% of HA sediments with the heavy P_1 fraction, which contains vascular elements and large nerve endings (513).

Microvessels isolated from homogenates of bovine (362), rat (382), or guinea pig brain (616) have high levels of HA with low HDC activity. In these fractions HA might be held either in endothelial cells or mast cells that are intimately associated with the cerebral vasculature.

C. Release

1. Release *in vitro*

Endogenous HA is released by K^+ -induced depolarization of cerebral slices via a Ca^{2+} - and temperature-dependent process (32, 360, 505, 519, 747). However, on this model the spontaneous efflux of HA is relatively high, as some part of the amine might originate from mast cells, and the K^+ -induced stimulation is of limited amplitude, resulting in only 50-100% increases in the HA level in medium. The 20 mM K^+ -induced release of endogenous HA from slices of mouse hypothalamus is enhanced at low concentrations of glucose, an effect largely prevented by tetrodotoxin (505).

Tritiated HA synthesized from [3H]His in slices from various brain areas is released by depolarizations induced by K^+ (25, 27, 28, 787, 788), electrical stimuli (781-783), or veratridine (25, 27). This occurs over a low spontaneous efflux and results in a 5- to 10-fold increase in [3H]HA in medium. Release of [3H]HA from depolarized slices is completely inhibited in the absence of Ca^{2+} or in the presence of 10 mM Mg^{2+} , suggesting that it results from the opening of voltage-sensitive Ca^{2+} channels (25, 782, 788). Doubling the external Ca^{2+} concentration diminishes the 30 mM K^+ -induced release of [3H]HA, presumably via inactivation of Ca^{2+} channels by an excess of intracellular Ca^{2+} (27). Conducted action potentials are presumably involved for a small part in the 30 mM K^+ -induced release, because the latter is only weakly reduced in the presence of tetrodotoxin (27). Neosynthesized [3H]HA is also released from depolarized synaptosomes (27) but not from mast cells (788). All these features are consistent with the idea that depolarization of histaminergic nerve endings induces HA secretion via mechanisms similar to those operating for other neurotransmitters.

Superfused brain slices preincubated in the presence of [3H]HA accumulate the amine against a small concentration gradient (tissue-to-medium ratio of 2) and release radioactivity on depolarizations induced electrically or by K^+ or veratridine (74, 475, 476, 512, 715, 716). Although the Ca^{2+} dependency of the process suggests that [3H]HA originates from neurons, its significance remains doubtful. Indeed, histaminergic neurons apparently lack selective reuptake systems for HA, and the extent of [3H]HA uptake in slices from various brain regions does not parallel the relative densities of HA

axons. Moreover, from the effects of neurotoxin-induced lesions it appears that a fraction of exogenous [3H]HA enters dopaminergic and 5-hydroxytryptamine (5-HT) neurons (695).

Compound 48/80, a mast cell degranulator, releases endogenous HA (788) and exogenous [3H]HA (716) but not neosynthesized [3H]HA (788) from hypothalamic slices. In contrast, reserpine, a drug interfering with storage processes in aminergic neurons, releases both endogenous HA (747) and neosynthesized [3H]HA (787) from these slices. These differential effects presumably illustrate the multicompartimentation of the amine in the brain and the fact that, in contrast with the neuronal pool, the slowly turning over pool is not readily labeled by [3H]His. Mast cells do not possess voltage-dependent Ca^{2+} channels in their plasma membrane and therefore do not release HA on depolarization (187, 716).

2. Release *in vivo*

Spontaneous and K^+ -induced release of endogenous HA into superfusates of the hypothalamus of anesthetized cats and freely moving rabbits was detected (560, 562). The spontaneous release appeared to vary rhythmically in hypothalamus but also in mammillary bodies or medial amygdaloid nucleus (583). After lesions of the ascending histaminergic pathway at the hypothalamic level, the HA content in the cerebral cortex transiently rises, which may reflect an impaired release resulting from the interruption of impulse flow (40, 231). Electrophysiological responses triggered in the cerebral cortex (640), hippocampus (284, 285), or nucleus accumbens (126) by large stimulations of putative afferent pathways were significantly impaired by iontophoretic application of HA receptor antagonists.

These observations may be taken as indirect evidence for a stimulation-induced release of endogenous HA *in vivo*.

3. Control of histamine release by autoreceptors and heteroreceptors

In slices from several regions of rat brain the release of neosynthesized [3H]HA induced by either K^+ (25-27), veratridine (25-27), or field electrical stimulation (781-783) is strongly inhibited on addition of exogenous HA in the external medium. In overflow experiments, the maximal inhibition of release may be as high as 80% with 30 mM K^+ stimulations (666) or nearly total with electrical stimulation (782, 783). Inhibition is more marked for depolarizing stimuli of low intensity (27). The autoinhibitory effect of HA appears to be a receptor-mediated effect, since it displays saturability [the half-maximal effective concentration (EC_{50}) of HA is ~0.1 μM], reversibility (it is suppressed by washing out the excess of exogenous HA from the preparation), and high pharmacological specificity, being mimicked or antagonized in a competitive manner by several agents displaying low if any activity at H_1 and H_2 receptors.

This last feature has led to the pharmacological definition of H_3 receptors (23, 25). The fact that H_3 receptors are directly located on histaminergic terminals was shown by various data: 1) the autoinhibitory effect of HA persists when the propagation of action potentials in the brain slice is blocked by tetrodotoxin, 2) it also persists in slices from kainate-injected striatum, and 3) it is also found with a synaptosomal preparation (26, 27). The extent of the autoinhibition can be modulated in a complex manner by changes in extracellular Ca^{2+} , suggesting that H_3 receptors regulate HA release via a control of Ca^{2+} entry (27).

The fact that selective H_3 -receptor antagonists modestly but significantly enhance [3H]HA release from depolarized slices and, when systematically administered, markedly enhance cerebral HA turnover indicates that H_3 receptors are tonically activated in vivo (23, 239, 519a). This observation might be related to the fact that endogenous HA concentration in human lumbar cerebrospinal fluid (CSF) ($\sim 0.4 \mu M$) is above the EC_{50} of HA at H_3 receptors (34, 388, 714). However, HA levels were found to be clearly lower when assayed by different methods (776a), and HA levels in ventricular CSF or extracellular fluid of the brain are not known.

Release of neosynthesized [3H]HA from rat brain slices and synaptosomes is inhibited by stimulation of muscarinic M_1 receptors (270), α_2 -adrenoreceptors (271, 310, 312), and opioid κ -receptors (271a). In contrast, [D-Ala²-N-Me-Phe⁴, Gly⁵-ol]enkephalin (DAGO), a specific agonist at μ -opiate receptors stimulates the 30 mM K^+ -evoked HA release from mouse brain slices (360). Hence not only auto- but also heteroreceptors appear to control the amine release.

D. Inactivation

1. Uptake

In several studies with brain slices or synaptosomes, no evidence for an active transport system for HA operating at histaminergic nerve endings could be found (324, 489, 664, 740). In contrast, uptake of labeled HA in brain slices, occurring against a limited concentration gradient, was reported in other studies (74, 475, 476, 512, 716, 778), some of which also demonstrated that the radioactivity could be subsequently released by depolarization (see sect. IIC). However, the maximum tissue-to-medium ratio was low, the energy dependence of the process not demonstrated, the regional distribution of this accumulation did not reflect that of HA neuronal markers, and finally release of accumulated [3H]HA was not regulated by H_3 autoreceptors. This suggests that no significant uptake occurred at HA nerve endings. On the contrary, recent lesion studies indicate that a fraction of [3H]HA is accumulated into serotonergic and dopaminergic neurons (695). In summary, HA neurons appear to be almost unique among monoaminergic neurons in that they lack a high-affinity reuptake system.

2. Transmethylation of histamine

In various tissues, HA catabolism occurs along two alternative pathways, i.e., transmethylation into *t*-MeHA catalyzed by histamine *N*-methyltransferase (HMT; EC 2.1.1.8) and oxidative deamination into imidazolacetic acid, catalyzed by diamine oxidase (histaminase, EC 1.4.3.6) (602, 603, 645). Contrary to an early report (698), only the former pathway operates in mammalian brain, as shown by the failure to detect diamine oxidase activity (103) or formation of labeled imidazolacetic acid after intracerebral administration of labeled HA; in contrast, both *t*-MeHA and its deaminated metabolite *tele*-methylimidazole acetic acid (*t*-MIAA) were detected (648, 649, 671). Low levels of *t*-MeHA are present in monkey and human CSF (389, 585, 722, 723).

Methylation also appears to be the main, presumably the only, pathway for the catabolism of endogenously synthesized [3H]HA in vivo (571, 601, 602, 648, 649, 672, 818) or in vitro after its depolarization-induced release (27, 788). Endogenous *t*-MeHA is present in brain at levels in the same range as those of HA and with a similar regional distribution (238a, 330, 336, 521, 522, 629). The large decreases in *t*-MeHA levels elicited by inhibition of either HDC (521, 522, 629) or HMT (339) imply that in vivo *t*-MeHA is mainly formed by HA methylation. However, a small contribution of the pathway involving decarboxylation of the natural amino acid *tele*-methylhistidine by HDC cannot be dismissed (674). Subcellular fractionation indicates that, in contrast to HA, *t*-MeHA is more abundant in the supernatant than in synaptosome-containing fractions (336), suggesting its predominantly extraneuronal formation.

tele-Methylhistamine is inactive at H_1 , H_2 (226), and H_3 receptors (25). The activity of HMT is high in the brain of various mammalian species in which its rather homogeneous regional distributions does not reflect that of HA neuron markers (36, 96, 628, 664, 771, 777). On subcellular fractionation, cerebral HMT is mainly recovered in the supernatant, with a rather minor contribution of the soluble fraction from synaptosomes (95, 423). Histamine *N*-methyltransferase is present in both glioma and neuroblastoma cell lines (236) as well as in cerebral microvessels (382). Neither lesion-induced degeneration of HA neurons nor intrahippocampal kainate (234) significantly affect telencephalic HMT (75, 237). In contrast, HMT was reduced in the striatum after local administration of kainate (699) and in the neurohypophysis after section of the pituitary stalk (785). Although HMT has not been visualized histochemically, all these data suggest that HMT is present in the cytoplasm of a variety of cerebral cells into which released HA has to enter (see sect. IID1). Diurnal (777) and hypertonic saline-induced (785) variations in neurohypophyseal HMT have been described.

Histamine *N*-methyltransferase from various tissues has been purified to homogeneity (88, 293, 460) and its properties reviewed (81, 786). The enzymes from brain and kidney have similar physicochemical, catalytic, and immunologic properties. They have a M_r of 30,000, a pI of 5.3, and an optimum pH for HA methylation of 7.5–9.0.

They catalyze the transfer of a methyl group from the universal donor *S*-adenosyl-L-methionine selectively to the *tele*-nitrogen of the imidazole ring of HA. The K_m s of both substrates are $\sim 10 \mu\text{M}$. No endogenous substrate other than HA has been identified. In vitro, HMT is inhibited by HA at concentrations $> 100 \mu\text{M}$ (47, 460, 746), but this may not have physiological relevance. Histamine *N*-methyltransferase is also inhibited by its two reaction products, i.e., *t*-MeHA (96, 438) and *S*-adenosyl-L-homocysteine (53, 529, 664, 837), with K_i s in the same range as the K_m s of its two substrates, implying a possible regulatory role (664). Although a different kinetic mechanism was proposed (748), a variety of features indicate that HMT functions with an ordered bi-bi-mechanism (30, 53, 219, 530).

In vitro, HMT can be inhibited by a large variety of drugs including H_1 -, H_2 -, and H_3 -receptor antagonists (for review see Ref. 786), with one of the most potent compounds being SKF 91488, a dimaprit analogue devoid of activity at receptors (58). In vivo, the most effective compounds to inhibit cerebral HMT are amodiaquin (664, 748) and, even more, metoprine (192). The latter decreases *t*-MeHA (339, 357, 835) and increases HA in rat brain (192, 838), confirming the key role of HMT in HA inactivation.

3. Oxidative deamination of *tele*-methylhistamine

The cerebral levels of radioactive *t*-MeHA formed from either labeled HA (648, 649, 671) or labeled His (571, 601) rise markedly in rodents treated with monoamine oxidase (MAO) inhibitors, such as pargyline, that are devoid of diamine oxidase inhibitory capacity. These drugs also increase endogenous *t*-MeHA (238a, 338, 522). This occurs without marked changes in levels of endogenous or labeled HA. Hence MAO seems responsible for the oxidative deamination of *t*-MeHA. The type B isoenzyme of MAO catalyzes the reaction, as shown with MAO inhibitors more selective than pargyline (329, 796).

Deamination of *t*-MeHA results in the formation of *t*-MIAA (645), which therefore represents the final product of HA metabolism in mammalian brain (389, 648, 649). Its level is reduced, although slowly, after inhibition of either HMT (339) or HDC (721). Probenecid, a drug inhibiting the active transport of deaminated metabolites of various monoamines from brain, does not apparently affect that of *t*-MIAA (387, 671). Endogenous *t*-MIAA is present in monkey and human CSF at levels slightly higher than those of *t*-MeHA (389, 585, 723).

4. Other inactivation pathways

The good agreement between turnover rates derived from the application of various methods indicates that formation of *t*-MeHA and its subsequent deamination constitutes the major if not the sole metabolic pathway for cerebral HA (see next section). Although mammalian

brain contains an *N*-acetylhistamine deacetylase (205, 297), endogenous acetylation of HA is not substantiated.

In invertebrates a major inactivation pathway for HA may consist of the formation of the peptidoamines γ -glutamyl-HA (703) or α -alanyl-HA, i.e., carbinine (20). Peptidoamines are also formed when HA and various amino acids are incubated with brain homogenates, but the physiological relevance of this observation has remained obscure (413, 599).

E. Turnover

Isotopic tracer methods, the first to be applied to the determination of HA turnover rate in brain, revealed that the half-life of the amine is a matter of minutes and can be altered almost instantaneously (170, 571). These early observations, which supported the contention that HA was released from neurons, have been essentially confirmed and extended with the development of various nonisotopic methods (for reviews see Refs. 258, 629).

1. Isotopic methods

With no selective uptake mechanism to mix radioactive HA to the endogenous stores, the latter must be labeled with the radioactive precursor to realize turnover studies. In early studies, [^3H]His was administered intracerebroventricularly in lightly anesthetized rats, and the fluctuations of the specific radioactivities of [^3H]HA and [^3H]His were typical for a precursor-product relationship in a single open compartment (170, 571). Analysis of this relationship using two different mathematical models led to values of 46 min (571) and 30 s (170) for the half-life of HA in whole brain. Neosynthesized [^3H]HA was localized in subcellular fractions containing nerve endings (571). However, the mode of administration of the tritiated precursor is unphysiological and results in a non-uniform labeling of various brain areas.

These drawbacks are avoided by intravenous administration of [^3H]His either in a pulse or at a constant rate (23, 660, 789). The mean half-life of HA in mouse brain was 46 min after constant rate infusion (660), a value similar to that found in rat brain (571), and 20 min after pulse injection (660). The values did not markedly differ between regions; however, there was a slightly shorter half-life in pons-medulla. The half-life of HA was much shorter in brain than in any peripheral organ (660).

2. Nonisotopic methods

Among the various experimental approaches that could theoretically be applied to the evaluation of HA turnover rate, only two have been extensively used; they consist of determining the rates of endogenous HA decline and *t*-MeHA elevation after inhibition of HDC and MAO, respectively.

After irreversible inactivation of HDC by α -FMH, HA levels decrease rapidly in mouse, guinea pig, and rat

brains (23, 235, 447, 507, 629). However, even a few hours after nearly total inactivation of HDC, the amine depletion is not complete, evidencing the presence of a resistant pool with a very slow turnover, the existence of which was already suggested in studies with less potent and reversible inhibitors (744, 745). The mean maximal HA depletion by α -FMH is $\sim 50\%$ but varies among CNS areas and animal species; in all species, no significant depletion occurred in the spinal cord (235, 507, 522, 629). The depletion of HA is rapid in a subcellular fraction containing nerve endings (23), indicating that HA turnover is rapid in neurons, but the cellular localization of the slowly turning over pool is still debated. In the brain of W/W^v mice, a mutant devoid of mast cells, HA levels are lower than in congenic normal mice and, in contrast to the latter, are almost completely depleted by α -FMH (447, 793, 833). However, this difference has not been confirmed in other studies (269, 335, 528).

The mean half-life of HA in the rapidly turning over pool is 30 min in rat, mouse, and guinea pig brains (23, 521, 522, 629). Whereas steady-state levels of HA vary markedly among regions, this is generally not the case for half-lives, but slightly higher values are found in the hypothalamus where HA perikarya are present.

After administration of pargyline, a MAO inhibitor, endogenous *t*-MeHA levels rise (238a, 337, 338, 521, 522, 629) at a rate that is likely to reflect that of HA release (571). From this rise, and with some assumptions, half-lives for HA can be derived that are generally in the same order as those obtained using synthesis inhibition or isotopic methods. Again the HA half-life is the longest in the hypothalamus, and the pargyline-induced rise in *t*-MeHA is negligible in spinal cord.

One potential limitation of these nonisotopic methods is that they require the administration of drugs in high dosages to completely block a metabolic pathway, and this could affect directly or indirectly the activity of histaminergic neurons. However, pargyline treatments, which are likely to affect several monoamines, do not generally modify HA steady-state levels (629) or turnover measured with [3 H]His (571).

3. Drug-induced changes in turnover

Histamine turnover in rat brain is reduced almost instantly on administration of barbiturates and a variety of hypnotics or anesthetics (37, 563, 571). Similar effects are observed with other "sedative" agents, such as the γ -aminobutyric acid (GABA)-mimetic drugs muscimol and benzodiazepines (506, 520), ethanol (356), and Δ^9 -tetrahydrocannabinol (519), the latter attributed to an inhibition of HA release. Other agents inhibiting HA release in vitro via stimulation of presynaptic histamine H_3 , α_2 -adrenergic, or muscarinic M_1 receptors reduce HA turnover in vivo (23, 270, 271). In contrast, reserpine, a drug interfering with the storage mechanisms of monoamines and releasing HA in vitro (747, 787), accelerates HA turnover (569). In vivo, blockade of H_3 receptors (23,

239, 519a) but not muscarinic or adrenergic receptors (270, 271) accelerates HA turnover, suggesting that only H_3 receptors are tonically activated in vivo.

Morphine (504), DAGO, a specific agonist at μ -opiate receptors (360), and [D-Ala², D-Leu⁵]enkephalin, a nonspecific agonist at δ -opiate receptors, but not ethylketazocine, an agonist at κ -opiate receptors (359), enhance HA turnover. The psychotomimetic agent phencyclidine has a similar effect, which is blocked by naloxone, an opiate receptor antagonist (357, 359). After the various treatments modifying HA turnover, Saeki and co-workers (504, 519, 520) found that the steady-state level of *t*-MeHA was modified in an apparently unrelated manner, suggesting that this level does not constitute a reliable turnover index.

III. DISPOSITION OF HISTAMINERGIC NEURONAL PATHWAYS

In 1974, the decrease of HDC activity found in many rat brain areas after lesions of the lateral hypothalamic area was the first evidence for the existence of an ascending HA neuronal pathway with widespread projections to almost all regions of mammalian brain (232). Ten years later, the exact localization of HA perikarya in the posterior hypothalamus was established immunohistochemically using HA (552, 707) and HDC antibodies (802, 803). During the same period, HA neurons had been identified in *Aplysia* brain by biochemical analysis of microdissected tissues (813).

A. Lesion Studies

The rough disposition of HA pathways in rat brain, initially established by lesion studies, is now confirmed and obviously largely extended by immunohistochemical data. Hence these studies, which are reviewed in detail elsewhere (666), are rapidly summarized here.

Unilateral interruption of the medial forebrain bundle leads to ipsilateral decreases in HDC activity (by 50–55%) and HA levels (by 25–30%) in telencephalic and diencephalic areas rostral to the lesion (231, 232). The existence of ascending fibers emanating from the same bundle was also deduced from the effects of discrete lesions of the afferents to the hippocampal region (40) and amygdaloid nuclei (60). From the analysis of a series of discrete lesions in the mesodiencephalon a localization of corresponding perikarya in the mammillary region of the hypothalamus (and the neighboring mesencephalic reticular formation) was suggested (233). Finally, the existence of a descending HA pathway emanating from the posterior hypothalamus and projecting rather heavily to various brain stem nuclei was proposed (572).

Recently, unilateral lesions with ibotenic acid in the vicinity of the mammillary bodies (where HA perikarya are located) induced bilateral reductions in HA levels in the hypothalamus and frontal cortex but an ipsilateral

reduction in hippocampus. In contrast, HA levels increased markedly in the neurohypophysis (501).

B. Immunohistochemical Tools

The precise localization of HA neurons could be established with the advent of several reliable immunohistochemical tools. High-affinity polyclonal antibodies to a highly purified, although not homogeneous, preparation of HDC obtained from rat fetal liver (731, 803) have found the largest applications in several laboratories. These antibodies cross-react with dopa decarboxylase in guinea pig (but not rat) brain (16, 732) and apparently cannot be used for immunohistochemistry in species other than rats. The antibodies for HDC developed earlier (224, 758) were less specific. Despite its specificity, a monoclonal antibody to partially purified HDC from rat stomach has found only limited histochemical applications because of its rather low affinity (573–575).

Polyclonal antibodies to HA raised against the amine either simply mixed with serum albumin (531, 821) or conjugated to proteins using aldehydes (707, 708) or carbodiimide (550–552) have been also used as histochemical tools. Among these, the latter appear as the most reliable tools, especially when the detection sensitivity is enhanced by using carbodiimide as a tissue fixative (550). In contrast, other HA antibodies were found to detect numerous immunoreactive fibers or neurons in areas, such as the median eminence (707, 821), in which they seem absent or very scarce (351), an artifact presumably related to cross-reactivity with histidine-containing peptides, such as luteinizing hormone-releasing hormone (LHRH) (64).

C. Localization of Histaminergic Perikarya: Tuberomammillary Nucleus

Strikingly consistent results were obtained in various laboratories regarding the localization of histaminergic perikarya, whatever the immunohistochemical tool used, i.e., either the anti-HDC monoclonal (573, 574) or polyclonal antibodies (207, 350, 606, 803, 804, 829) as well as the anti-HA antibodies (550–552, 707, 708). Hence HA perikarya, mostly large cells, were found to be confined to the tuberal region of the posterior hypothalamus in an area where a group of Nissl-stained magnocellular neurons had been detected earlier and collectively named the tuberomammillary nucleus (TM) (165, 474; Fig. 1). Two groups of Nissl-stained magnocellular neurons were also detected later in the same area by Bleier et al. (80), who named them the caudal magnocellular nucleus (CMC) and the tuberal magnocellular nucleus (TMC). The same region is included in an "efficient area" defined by analyzing combined lesion data and proposed to contain HA perikarya projecting to the telencephalon (233). Other previous data are consistent with this localization: the neurotoxin kainate decreases HDC in this area, presumably by ablating HA perikarya, whereas colchicine has an opposite effect, presumably by blocking the enzyme axonal transport (233).

Whereas in previous studies HA perikarya were considered to belong to several distinct nuclei, generally named after Bleier et al. (80), Ericson et al. (207), in the most comprehensive anatomic study of this area performed at the light-microscopic level with the anti-HDC antibodies of Watanabe et al. (803), provided convincing evidence for the HA perikarya making up one continuous cell group. The latter, named the TM after Morgan (474) and a previous study of the same laboratory (411), was divided in several subgroups, generally in agreement with studies of other laboratories, although the nomenclature differs (for a correspondence see Fig. 1).

The medial tuberomammillary subgroup (TMM) is constituted of ~600 neurons situated on each side of the mammillary recess. It can itself be subdivided into 1) a dorsal part (TMMd) corresponding to the TMC of Bleier et al. (80), i.e., an isolated group of cells extending over 1.5 mm along the tip of the third ventricle between the dorsal premammillary nucleus and the dorsomedial nucleus; and 2) a ventral part (TMMv) close to the ventral surface of the brain just rostral to the medial mammillary body, occurring as a cluster of cells located dorsolaterally to the infundibular nucleus and the mammillary recess. This cluster is bridged (207, 827) by isolated immunoreactive cells with the ventral tuberomammillary subgroup (TMV).

The TMV, the largest one comprising ~1,500 mostly magnocellular neurons, is subdivided by the mammillary bodies into 1) a rostral part (TMVr), corresponding to the CMC of Bleier et al. (80), situated just in front of the lateral mammillary nucleus; and 2) a caudal part (TMVc), corresponding to the posterior caudal magnocellular nucleus of Bleier et al. (80), situated behind the lateral and medial mammillary bodies and the supramammillary nucleus.

The diffuse part of the tuberomammillary nucleus (TMDiff) is constituted by a small number (~100) of HDC-immunoreactive cells scattered within or between various hypothalamic nuclei in the lateral hypothalamic area, the posterior hypothalamic area, the perifornical area, and the supramammillary and dorsomedial nuclei. Most of them were detected in previous immunohistochemical studies (573, 574, 707, 708, 803, 804), but they were only recently considered (207, 411) as belonging to a single subset.

Histamine perikarya are immunodetectable in rat hypothalamus during late fetal stages (35, 605) and can be cultivated for several days *in vitro* (550).

Although most anatomic studies were performed in rats, the TM was first identified in Nissl-stained sections of the dog hypothalamus (474) and seems present in all mammals, becoming more differentiated in primates and most extensive in humans (165, 411). With the use of antibodies against HA, perikarya were also localized in the mammillary region of guinea pigs: they seem more numerous than in rats, being also found between the medial and lateral mammillary nuclei as well as between the premammillary nuclei (7). In cat hypothalamus, magnocellular neurons becoming immunoreactive to 5-HT antibodies after treatments with 5-hydroxytryptophan (5-

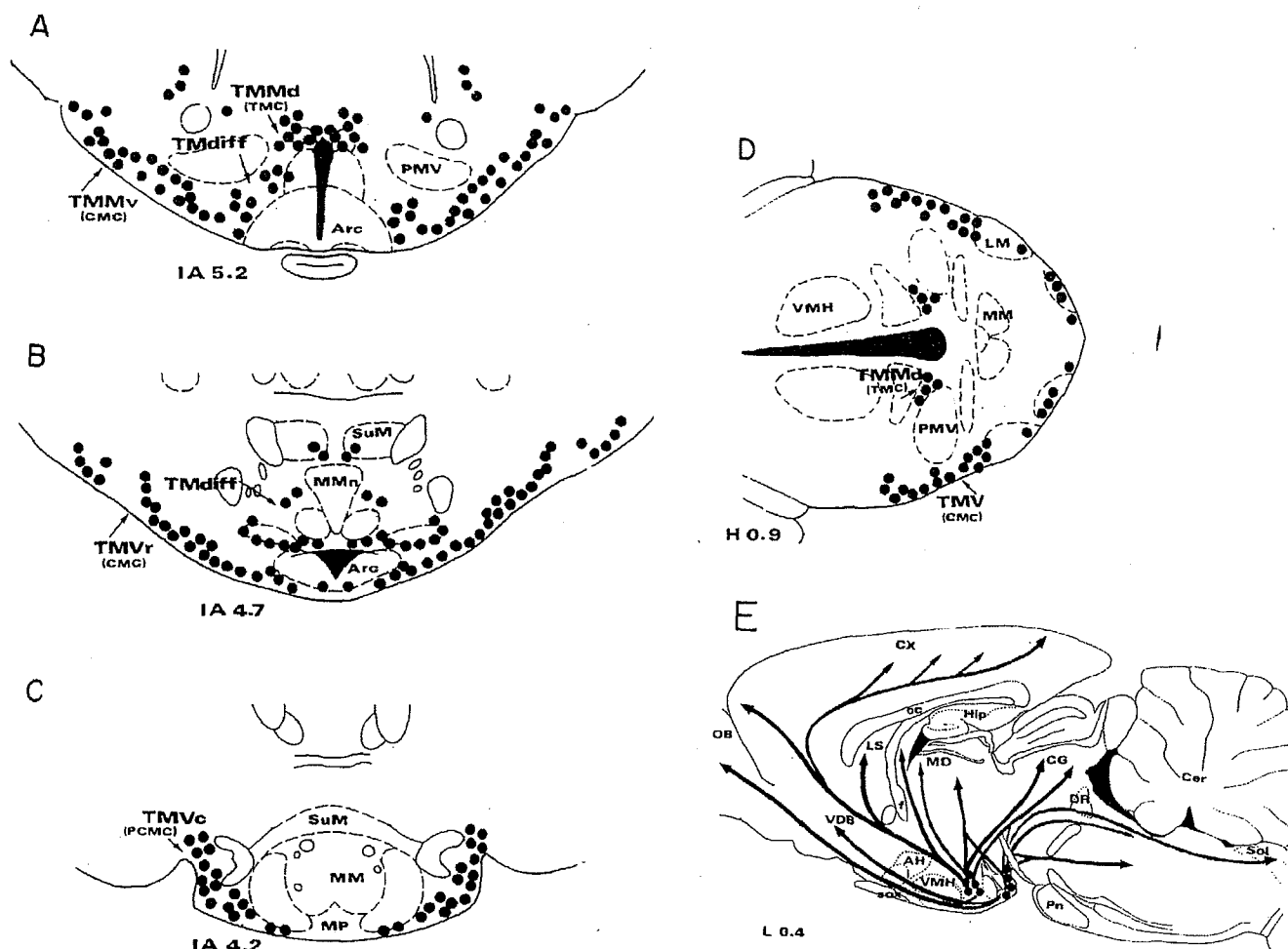


FIG.1. Localization of histaminergic perikarya (closed circles) in tuberomammillary nucleus and disposition of main histaminergic pathways (arrows) in rat brain. Sections represented according to atlas of Paxinos and Watson (553a). The subgroups of perikarya in tuberomammillary nucleus are designated according to Morgan (474), Diepen (165), and Köhler et al. (411), and corresponding nomenclature according to Bleier et al. (80) is indicated within parentheses. A, B, and C: frontal sections at indicated levels of caudal hypothalamus. D: horizontal section through caudal hypothalamus. E: sagittal section of brain. Abbreviations of perikarya subgroups: CMC, caudal magnocellular nucleus; PCMC, posterior caudal magnocellular nucleus; TMC, tuberal magnocellular nucleus; TMDiff, tuberomammillary nucleus diffuse part; TMMd, medial tuberomammillary subgroup dorsal part; TMMv, medial tuberomammillary subgroup ventral part; TMV, ventral tuberomammillary subgroup; TMVc, ventral tuberomammillary subgroup caudal part; TMVr, ventral tuberomammillary subgroup rostral part. Other abbreviations: AH, anterior hypothalamic area; Arc, arcuate nucleus; cc, corpus callosum; Cer, cerebellum; CG, central gray; CX, cerebral cortex; DR, dorsal raphe nucleus; f, fornix; Hip, hippocampus; LM, lateral mammillary nucleus; LS, lateral septum; MD, mediodorsal thalamus; MM, medial mammillary nucleus medial part; MMn, medial mammillary nucleus median part; MP, medial mammillary nucleus posterior part; OB, olfactory bulb; PMV, premammillary nucleus ventral part; Pn, pontine nuclei; Sol, nucleus of solitary tract; Sox, supraoptic decussation; SuM, supramammillary nucleus; VDB, nucleus of vertical limb of diagonal band; VMH, ventromedial hypothalamic nucleus.

HTP) seem to correspond to HA neurons and extend from the suprachiasmatic nucleus to the caudal end of the hypothalamus (632, 636, 637). Histamine-immunoreactive perikarya were also detected in the human mammillary region (549, 549a). In all these species the HA magnocellular neurons seem less aggregated than in rats but otherwise display very similar features.

In one study immunoreactive HDC (irHDC) horizontal cells were detected in the guinea pig retina (17), but this could not be confirmed using an anti-HA antibody (7).

D. Morphology of Histaminergic Neurons

The HA neurons of the TM display a series of characteristic features, as revealed in the various immunohistochemical studies at the light-microscopic level (see sect. IIIC) or electron-microscopic level (296, 825, 829).

Most of them are large (25–35 μ m) neurons, particularly in the TMV (since the TMM contains a large number of medium-sized cells), with a round unindented nucleus, a well-developed Golgi apparatus, and a relatively large

amount of karyoplasm. Very similar ultrastructural characteristics are found in noradrenergic or serotonergic perikarya as well as in the cholinergic perikarya of the basal nucleus of Meynert.

Another characteristic feature at TM cells is their dendritic processes comprising two to three thick primary dendrites dividing into long (100-150 μ m) secondary dendrites, with few spines and axodendritic synaptic contacts. The dendritic trees of adjacent neurons overlap each other. In one study it was observed that the dendrites narrowed down into varicose fibers filled with small vesicles similar to synaptic vesicles, and it was hypothesized that exocytosis might occur at this level (445), but this was not confirmed in another study in which the varicose fibers emerging from the emission cones of dendrites were identified as axons (825).

Another very characteristic feature is the close interaction of dendrites with glial elements in the mammillary recess and the ventral surface of the brain in a way suggesting that the dendrites penetrate into the ependyma and come into close contact with the CSF. The exact functional significance of this peculiar organization is still obscure, but it has been proposed that HA neurons might either release their secretions into the CSF (445) or respond to CSF-borne substances (606).

Finally, in one ultrastructural study, both myelinated and unmyelinated irHDC varicose axons, making few typical synaptic contacts, were observed in the TMV (294). This was interpreted as evidence for a mainly non-synaptic release of HA, similar to that proposed for other monoamines (57), but the relationships of these elements with the varicose dendrites of Maeda et al. (445) remains to be clarified.

E. Other Putative Transmitters in Histaminergic Neurons

The HA neurons in TM are characterized by the unusual presence of a large variety of markers for other neurotransmitter systems, some of which evidenced before or independently from the demonstration of HA itself.

Glutamic acid decarboxylase, the GABA-synthesizing enzyme, was first evidenced in TM neurons projecting to the cerebral cortex by Vincent et al. (791), and its colocalization with the vast majority of irHDC neurons (679, 734, 825) was shown soon later.

In a parallel manner, Nagy et al. (478) evidenced in TM neurons the presence of adenosine deaminase, a cytoplasmic enzyme that might be responsible for the inactivation of the putative neurotransmitter adenosine. Presence of this marker in the vast majority of irHDC perikarya was demonstrated soon after (553, 679, 700). Tuberomammillary nucleus neurons also express binding sites for a putative ligand of adenosine uptake sites (477).

A majority of irHDC neurons also stain with antibodies against galanin, a 29-amino acid neuropeptide (410, 466, 700). Interestingly galanin is also colocalized

with other amines, i.e., catecholamine, 5-HT, and acetylcholine in other cerebral neurons (466).

Also a majority of TM neurons stain with antibodies raised against the opioid heptapeptide (Met⁵)enkephalyl-Arg⁶-Phe⁷, suggesting that they express the proenkephalin A gene (411, 822).

Staining of at least a fraction of TM neurons with antibodies against two other neuropeptides, i.e., substance P (411) or thyrotropin-releasing hormone (TRH) (688) was also reported.

Another characteristic feature of a rather large subpopulation of TM neurons is the presence of high MAO B activity, possibly related to deamination of *t*-MeHA (392, 393, 444, 445, 700, 730). This subpopulation, representing ~60% of neurons expressing both HDC and adenosine deaminase, could be the same as that expressing enkephalins (730).

Finally, a fraction of TM neurons have the capacity to uptake and decarboxylate 5-HTP into 5-HT (which is then detected immunohistochemically) but not to synthesize 5-HT after tryptophan administration (445, 632, 637, 700). This suggests that some TM neurons express not only HDC, for which 5-HTP is not a substrate, but also the aromatic amino acid decarboxylase (EC 4.1.1.28) and thereby resemble the peripheral APUD cells (554).

The fact that such a high number of neurotransmitter markers are apparently expressed by the same TM neurons raises several comments: 1) these colocalizations have been established by purely histochemical approaches and require confirmation by other approaches; 2) the biological significance of some markers, e.g., adenosine deaminase or 5-HTP uptake and decarboxylation activities, is not fully clarified; and 3) the delineation of neuronal subpopulations within the TM, taking into account which among the eight markers listed above are coexpressed by each cell, has only started (410, 679, 700). Finally, and most importantly, establishing the functional significance of the colocalization of such a high number of messengers in a single population of neurons still remains an important and exciting challenge.

F. Pathways and Projection Fields of Histaminergic Neurons

Although some fibers were detected in the early immunohistochemical studies (552, 573, 574, 707, 708, 731, 805), it is only recently that technical improvements have started to reveal the extensive networks of irHDC (350) and irHA (7, 551) fiber systems in brain that were already suggested by lesions (232). This information has been complemented by that provided by retrograde tracing studies, sometimes performed before the realization that HA perikarya were located in the TM.

Histamine neurons constitute long and highly divergent systems projecting in a diffuse manner to many cerebral areas (232), with immunoreactive varicose or non-varicose fibers being detected in almost all regions of frog (7a), rat (350, 551), guinea pig (7), tree shrew (6a), or human brain (549, 549a). Despite initial suggestions that

the various TM subgroups might have distinct projection fields (708, 709), more recent retrograde tracing studies have established that TM neurons are not organized in a highly topographic way, since individual neurons give rise to projections to widely divergent parts of the forebrain, cerebellum, and mesencephalon (207, 411).

Panula et al. (551) distinguished two ascending pathways in rat brain. The ventral pathway runs at the basal surface of the brain toward the horizontal limb of the nucleus of the diagonal band and then to the medial septal nucleus or the olfactory tubercle and bulb, with a large fraction of the fibers crossing the midline in the retrochiasmatic area. The dorsal pathway runs along the lateral side of the third ventricle and contributes to fibers ending in thalamus and rostral forebrain structures (Fig. 1).

Moderately dense HA fibers are quite evenly distributed in all areas and layers of the cerebral cortex (7, 350, 551, 707, 708, 735, 803). In human cerebral cortex they appear to be most abundant in the external layers where they run in parallel to the surface (549, 549a). Deafferentation studies have established that they are extrinsic (41, 232, 735), and retrograde tracing studies showed that they emanate from the TM (207, 411, 478, 632, 708, 709, 784, 791), ascending through the medial forebrain bundle itself (232), which contains numerous fibers in rats (350, 551) or in guinea pigs an area between this bundle and the optic tract (7).

From studies combining lesion and biochemical (231-233) or immunohistochemical (735) analysis of HDC, it appears that the cerebral cortex receives predominantly ipsilateral projections of HA fibers. However, a minor participation of a contralateral projection, representing only about one-fifth to one-third of the total, was shown by retrograde tracing (411, 478, 735, 791) and antidromic activation studies (604). Midline crossing of these fibers occurs at the level of the retrochiasmatic area, the optic chiasma, and in the supramammillary region (350, 551) and was overlooked in combined unilateral lesion and biochemical studies (231, 232), presumably because of its limited extent and inherent individual variation among control (nonlesioned) animals. The extent to which crossing of fibers originating from the TM occurs seems to vary according to the innervated brain area, but there is, in most cases, a majority of ipsilateral fibers (207, 411).

In a variety of other telencephalic areas, immunohistochemical studies, sometimes combined with retrograde tracing, have shown long ascending connections between perikarya in the TM and the olfactory bulb (mainly in the external plexiform layer), hippocampus (mainly in dentate gyrus and subiculum), nucleus accumbens, globus pallidus, and amygdala (7, 207, 350, 550, 551, 708, 709, 828). In the caudate-putamen, fibers are surprisingly scarce when detected with anti-HA antibodies (551) but are considerably more numerous when detected with anti-HDC antibodies (350, 803). This general organization of HA pathways is in agreement with previous deafferentation or focal lesion-induced changes in HDC in some of these areas, i.e., the amygdaloid complex in which a very rich HA innervation is present (60) or the hippocampus (40).

These studies suggested that, in rats, HA fibers reach the amygdaloid complex via the ansa peduncularis and the hippocampus via a dorsal route comprised of the fimbria, fornix superior, and cingulum; in agreement immunoreactive fibers seem abundant in rat fimbria (350, 551) but very scarce in the guinea pig fimbria and fornix (7).

In the diencephalon, the most densely innervated part of the brain, various nuclei of the anterior and medial hypothalamus, e.g., the suprachiasmatic, supraoptic, paraventricular, arcuate or ventromedial nuclei, as well as of the thalamus, e.g., paratenial and paraventricular nuclei, contain numerous HA fibers (7, 350, 551, 552, 573, 708, 803). Hypothalamic nuclei contain high levels of HA and HDC activity (98, 567), with the latter being decreased after more caudal hypothalamic lesions (232, 233). In the median eminence only, scarce immunoreactive fibers are detected, mainly in the internal layer (7, 350, 351, 551), confirming that the high HA level in this area mainly corresponds to mast cells (567). In the hypothalamus, fibers in moderate density occur in the posterior lobe but seem absent in the other lobes (7, 350). Bilateral projections from the TM to widespread regions of the hypothalamus were evidenced by retrograde tracing (701).

Finally, a long descending HA system, also arising from the TM and projecting to various brain stem structures and the spinal cord, was evidenced by lesion (233, 572), immunohistochemical (7, 350, 352, 551, 708, 795), and retrograde tracing studies (207, 632). Interestingly, double tracing studies have suggested that a single TM neuron might send both ascending and descending projections (207), but this is not consistent with other observations (632, 733). Fibers travel caudally in association with the medial longitudinal fasciculus in rats (795) and with the dorsal fasciculus and medial periventricular gray in guinea pigs (7). The most densely innervated structures in the brain stem are the mesencephalic nucleus of the trigeminal nerve, the central gray, the colliculi, and the nucleus of the solitary tract, whereas other cranial nerve nuclei seem less abundantly innervated (7, 350, 352, 572). With the use of antibodies against HA, moderate to dense networks were observed in the substantia nigra and raphe nuclei of guinea pigs (7) as well as of rats (551) in agreement with biochemical (572) but not immunohistochemical data obtained with antibodies against HDC in rats (350). A direct projection of the TM to the locus coeruleus was shown by retrograde tracing (632, 724).

In the cerebellum, irHA fibers are sparsely distributed in all cortical layers and nuclei (7).

In the dorsal horn of the spinal cord (mainly the cervical part), fibers originating from the TM are moderately abundant and some cross the midline (7, 795).

Immunoreactive HA fibers are observed in the wall of intracerebral blood vessels in rats (710) but not in guinea pigs (7).

G. Ontogeny of Histaminergic Neurons

The ontogeny of irHA (35) and irHDC neurons (605) was recently studied in rat brain. The first irHA perikarya were seen on embryonic day 13 in the border of

metencephalon and mesencephalon and on *day 15* in the ventral mesencephalon, metencephalon, and myelencephalon. From these scattered cells a transient ascending and descending fiber system starts to develop on embryonic *day 15* but has completely disappeared by *day 20*. In contrast, in the basolateral hypothalamus, irHA (35) and irHDC cells (605) were first detected on embryonic *day 16* when they had stopped their mitotic division. The differentiation of immunoreactive neurons in the various subgroups of the caudolateral part of the tuberomammillary nucleus seems largely achieved by embryonic *day 20*, whereas the appearance of the dorsal subgroup in the medial part of the nucleus only occurs during the last prenatal days. Adenosine deaminase is first detected in tuberomammillary neurons on embryonic *day 18* (679).

The development of most irHA fibers takes place during the first two postnatal weeks (35), which coincides with the developmental pattern of HDC activity taken as a selective marker of HA neuronal pool (457).

In contrast, irHA mast cells are most numerous on postnatal *day 4* (when they are mostly located in the hippocampal area), and after that, their number gradually decreases (35), a pattern that explains changes in HA levels, as proposed (457).

H. Afferents to Histaminergic Neurons

Little is known about the sources and biochemical identity of neuronal afferents to HA neurons, namely because their location as a thin sheet of perikarya at the basis of the brain severely restricts the application of retrograde tracing substances. Anterograde tracing studies had shown that substantial projections to the posterior hypothalamus arise from the olfactory tubercle, subiculum, septum, medial preoptic area, and dorsal tegmentum (725), but their actual projections to HA perikarya were not established. Recently, however, Wouterlood and colleagues have started to apply to this problem a double-label immunocytochemical method (826), using antibodies against HDC and *Phaseolus vulgaris* leucoagglutinin, an anterograde tracer. In this way projections from the infralimbic division of the prefrontal cortex (830), all nuclei of the septum diagonal band complex (except the medial and lateral parts of the horizontal limb of the diagonal band) (828), and the medial preoptic region of the hypothalamus (827) were evidenced at the light-microscopic level. The pathways for the afferent fibers could be traced and varicosities on these fibers observed in proximity to irHDC cell bodies and dendrites, suggesting the possible occurrence of synaptic contacts. Because the areas of origin of these afferents receive, in most cases, heavy histaminergic inputs, a reciprocal control with TM neurons was postulated. However, blockade of postsynaptic H_1 and H_2 receptors does not affect HA turnover in cerebral cortex (239).

Afferent serotonergic and noradrenergic fibers were also described in the TM (207). Although the existence of direct connections remains to be established, the

presence of α_2 -adrenergic receptors on HA cells (271) may reflect a noradrenergic input.

IV. NONNEURONAL STORES OF HISTAMINE IN BRAIN

Outside the brain mast cells represent a major site of HA storage, and their exposure to antigen (via interaction with immunoglobulin E) or to histamine releasers (e.g., compound 48/80, a basic polymer) leads to extrusion of HA, heparin, and proteases contained in their granules. In peripheral tissues, mast cells are often found in connective tissue, in proximity to vascular elements, and for a long time they were thought to be absent from brain, which contains very little connective tissue. In the early 1970s they were progressively detected by their metachromatic staining by dyes such as toluidine blue (111, 189, 342, 390, 419, 524, 559), and their significant contribution in cerebral HA levels was proposed (457, 654). However, although the existence of this nonneuronal pool of HA is generally admitted, its relative quantitative importance is still debated (328, 584), the function of brain mast cells essentially is unknown (747a), and the existence of additional nonneuronal pools is postulated.

A. Mast Cells in Brain

In peripheral tissues, mast cells are essentially defined by their morphological properties, e.g., metachromasia or alcian blue staining of their very large granules. However, they constitute a heterogeneous population with two main subtypes, the connective tissue and the less typical mucosal mast cell (206). The mast cell subtypes are distinguished by their morphology, staining properties, HA content, composition (e.g., intragranular proteases), and sensitivity to HA releasers (206).

In brain, mast cells, detected by their metachromasia (111, 189, 190, 332, 419, 524, 559), the HA, and in rats 5-HT histofluorescence (199), HA immunoreactivity (7, 550, 552, 707), or their ultrastructure (166, 343), are present in a large number of species (190), including humans (199, 202). Mast cell numbers and localization in brain are characterized by striking variations according to regions, species, individuals, periods of the year, age, sex, side of the brain, and even handling of the animal (for review see Refs. 328, 332, 559, 747a), which may be real or related to the limited reliability of the staining procedure. Nevertheless, from most studies, mast cells seem generally abundant in leptomeninges, pituitary, pineal gland, area postrema, or median eminence but also occur in the brain parenchyma itself, mainly the grey matter, where, similar to their counterparts in peripheral tissues, they are distributed along vessels. The reported number of mast cells in rat brain varies between a few hundreds to >10,000, among which a fraction as large as 80% is found in the thalamus, particularly its lateral nuclei (189, 190, 251, 332, 559). However, in other species the distribution might differ with, for instance, a high density in the cerebral cortex of cats (343) or chimpanzees (190).

The fraction of rat brain HA contained in mast cells has been estimated to be ~50% from lesion and subcellular fractionation studies (231, 457, 654) as well as from mast cell counts combined with HA assays (332); however, others suggested this fraction to be negligible (584). Studies of mutant *W/W^v* mice deficient in mast cells did not clarify this issue, because their cerebral HA levels were found to be decreased compared with corresponding controls in two laboratories (447, 793, 833) but not in two other laboratories (335, 528).

A large fraction of HA might be held in mast cells in the neonatal rat brain (457) in which they seem more numerous than in the adult (7, 190, 213). This feature would explain 1) the relatively high HA level just after birth (555, 619, 669, 749, 836); 2) the distinct properties of HA-storing granules in neonatal brain, which sediment like those of mast cells (457, 565, 836); 3) the low turnover of HA, which resembles more that of the amine in typical mast cells than in the adult brain (457); and 4) the clear *in vitro* releasing effect of compound 48/80 (457), whereas in the adult brain this effect only occurs with slices of regions, such as the median eminence, where mast cells are abundant (567). Mast cells could proliferate in the neonatal brain under the action of nerve growth factor (11).

Ultrastructural studies (166, 343, 344, 346-348, 713) have all confirmed the close association of brain mast cells with blood vessels and allowed Ibrahim (343) to distinguish two types among these cells. Type I cells are those with morphological properties, including metachromasia, identical to those of typical, i.e., connective tissue, mast cells, which would be those reported by most investigators. Type II mast cells were later called neurolipomastocytes because of the high lipid content of their large granules, which are stained by toluidine blue but are not metachromatic or alcianophilic, although they otherwise display close ultrastructural similarity with typical mast cells. Neurolipomastocytes, which seem more numerous than typical mast cells, enter the brain with pial blood vessels and are always associated with arterioles or venules at the site of vessel branching where autonomic innervation of pial vessels is the densest (166, 713). In these cells, the presence of HA has not been directly demonstrated, but they degranulate under the action of compound 48/80 (166, 347, 348). As mast cells in peripheral tissues (496, 702, 820), neurolipomastocytes in pial arteries of rats and rabbits are autofluorescent cells often situated in apposition with varicosities from nerves of sympathetic and other origin, suggesting that their function (secretion?) might be neurally controlled (166, 747a).

Although the function of cerebral mast cells is not established, the localization, innervation, and content of these cells suggest their participation in the regulation of cerebral blood flow and inflammatory reactions (747a).

B. Other Nonneuronal Stores

Histofluorescence studies have suggested the association of HA with cerebral vascular elements (204, 332). In

agreement, a relatively high HA level is found in isolated cerebral microvessels in which it is associated with a low HDC content, suggesting that, therein, the amine turns over slowly (362, 381, 382, 616). Because this fraction did not contain metachromatic cells, it was assumed that HA was held in endothelial cells (616), which may contain a still poorly characterized pool of "nascent HA," the formation of which is induced by hormones or various inflammatory agents (370, 646).

The unexpected rise in cerebral HA level that accompanies several large lesions (168, 418) may correspond to this poorly clarified process.

V. HISTAMINE RECEPTORS IN BRAIN

The idea that the various actions of HA on peripheral tissues were mediated by more than one receptor subtype emerged progressively. It was first realized that the antihistamines (now termed H_1 -receptor antagonists), the first of which was developed in France in 1937 (87), did not block uniformly all actions of HA, leaving for instance gastric acid secretion unaffected. In 1966, Ash and Schild (31), demonstrating that these various actions could also be differentiated to a certain extent by agonists, clearly postulated the existence of the second (H_2) receptor subtype that was "proven" in 1972 with the development by Black et al. of burimamide (77), the first "selective" antagonist (in the sense that it has no significant affinity for H_1 receptors). Three years later, both H_1 and H_2 receptors were shown to be present in mammalian brain where they control cAMP formation (56, 618) and the firing rate of cortical neurons (279). In 1976, the association of H_2 receptors with adenylate cyclase (298) and that of H_1 receptors with the phosphatidylinositol cycle (361) were shown. Finally, in 1983, Arrang et al. (25) proposed the existence in brain of the H_3 receptor (for which, ironically, burimamide was found to be the most potent antagonist available at this time), which was "proven" in 1987 with the design of fully selective agonist and antagonist compounds (23).

The experimental definition of the three HA receptor subtypes relies on the use of selective agonists and antagonists that are now available, except, however, a highly selective H_1 -receptor agonist. Various aspects of the field of cerebral HA receptors were recently reviewed (105, 137a, 256, 304, 305, 658, 659).

A. Histamine H_1 Receptors

1. Molecular properties

The antagonist [3H]mepyramine was introduced in 1977 as the first selective radioligand for H_1 receptors (313) and still displays advantages over other tritiated ligands, i.e., the antidepressants [3H]doxepin (3, 375, 739, 752, 757) or [3H]mianserin (558) as well as (+)-*N*-methyl-4- $^{[3H]}$ methyl-diphenhydramine, a quaternary derivative of diphenhydramine (759, 760), that appear less

selective. A mepyramine derivative [125 I]iodobolpyramine (78, 414) is also a highly selective probe for the H_1 receptor, which it labels reversibly with high affinity and provides a 50-fold increase in detection sensitivity over [3 H]mepyramine (414, 622). Tritiated mepyramine was proposed (589, 591) for H_1 -receptor labeling in brains of living mice and as a means of predicting the potential sedating ability of H_1 antihistamines and a variety of antipsychotics and antidepressants (589). This test is currently applied to assess the brain penetration ability of potentially nonsedating H_1 -receptor antagonists (6, 109, 429, 620).

The pharmacology of H_1 receptors differs among animal species, since some antagonists, e.g., mepyramine, display significantly lower affinities in rat (or mouse and rabbit) brains than in guinea pig or human brains (3, 73, 117, 120, 121, 306, 311, 377, 414, 755, 797). This rather unusual species difference is confirmed when a functional response, i.e., HA-induced glycogenolysis, is considered (590). The binding of HA to H_1 receptors is inhibited, although to a limited extent, by guanylnucleotides (119, 483, 622), and the effect is lost on solubilization (752). This suggests that the H_1 -receptor is regulated by a G protein that is presumably distinct from the N_i protein, because pertussis toxin is inactive on HA binding (483). Sodium ions also decrease HA affinity at H_1 receptors, but the functional significance of this effect is unclear (119). Both thiol-alkylating (240, 834) and the disulfide bond-reducing agents (173-175) stabilize a fraction of the H_1 receptors in a high-affinity state for HA and full agonists, presumably by modifying a critical cysteine residue(s) located outside the HA binding domain (834).

The H_1 receptor can be solubilized using digitonin (240, 243, 752) or other detergents (223, 799). In the solubilized state, it is retained on a wheat-germ agglutinin column, indicating its glycoprotein nature (240), and the molecular sizes of the receptor-detergent complexes determined by gel filtration are 430,000 (752) and 670,000 (223).

The molecular size of the H_1 receptor from various tissues, as determined by target size analysis, ranged from 100,000 to 160,000 (424, 798). A [3 H]mepyramine binding site abundant in rat liver membranes has been partially purified, but it does not pharmacologically correspond to the H_1 receptor (223).

A mepyramine derivative [125 I]iodoazidophenpyramine is an extremely potent H_1 -receptor antagonist ($K_D = 10$ pM) that, after irradiation, selectively and irreversibly labels a 56-kDa subunit, presumably representing the ligand binding domain of the receptor in guinea pig brain (622, 624) as well as in a variety of other tissues (624). In contrast, the H_1 -receptor subunit labeled in heart has a larger apparent mass, suggesting that various tissues may express distinct isoforms of this receptor (622).

2. Distribution in central nervous system

The number of cerebral H_1 receptors varies among species but the mean density, i.e., ~ 100 fmol/mg mem-

brane protein, is in the same range as that of receptors of other neurotransmitters, which are generally more abundant in brain than HA (121, 307, 311, 375, 414, 592, 622, 623). Not only the density of H_1 receptors but also their regional distribution markedly varies between animal species, with, for instance, the cerebellum being the densest area in the guinea pig and the least dense in rat or human brain (121, 375). In human brains, the highest [3 H]mepyramine binding is found in the neocortex and various limbic structures (121, 375). These species differences reflect only partly those in histaminergic innervation that appear much less marked (7, 551).

Several cell types might express the H_1 receptor in brain. Kainate lesions decrease H_1 receptors in guinea pig cerebellum, suggesting their association with neuronal membranes (544), but they do not affect them in several areas of rat brain, which may reflect a predominantly nonneuronal localization (122). Although H_1 receptors are present on cerebral microvessels, they represent only a small fraction of the brain's total content (557). The H_1 receptors have also been located on human astrocytoma cells (483).

In contrast, the predominant localization of H_1 receptors to grey matter areas and their highly heterogeneous and sometimes laminar distribution, as established autoradiographically at the light-microscopic level using [3 H]mepyramine (543-545) or [125 I]iodobolpyramine (86, 414), are consistent with a major neuronal localization.

A detailed atlas of H_1 receptors in guinea pig brain has been established using [125 I]iodobolpyramine, which, like other 125 I probes, displays distinct technical advantages over 3 H probes in autoradiographic studies (86). In the cerebral cortex, H_1 receptors are present in all areas and layers, with a higher density in lamina IV. In the hippocampal formation, H_1 receptors display a laminated pattern of distribution and are the most abundant in the dentate gyrus (hilus and molecular layer) and in several areas of the subiculum and commissural complex. In the amygdaloid complex, the highest densities are found in the medial group of nuclei. In the basal forebrain, the striatum is faintly labeled, whereas the nucleus accumbens, islands of Calleja, and most septal nuclei are highly labeled. In the thalamus, H_1 receptors are present in high density, particularly in the anterior, median, and lateral groups of nuclei. In the hypothalamus the labeling is highly heterogeneous with high densities in, for example, medial preoptic area, dorsomedial, ventromedial, and most posterior nuclei, including the tuberomammillary complex in which histamine perikarya and short axons are present. In the cerebellum the molecular layer is densely labeled (86, 414, 543), but H_1 receptors are also detectable in the granular layer and inner nuclei (86, 414). In normal mice, the pattern is similar, and changes occurring in mutant strains are compatible with a predominant localization to Purkinje cells (621). In guinea pig mesencephalon and lower brain stem, H_1 receptors are particularly abundant in the nuclei of origin of most cranial nerves, in areas containing the perikarya of the catecholamine and 5-HT systems, and in various areas associated with vegetative reflexes,

e.g., the area postrema. The H_1 receptors are abundant in cochlear nucleus in rats (543) and mice (221). In the spinal cord, the highest density is found in the external layers of the dorsal horn in guinea pigs (86) as well as in monkeys (502, 503).

There are several discrepancies between the distributions of HA terminals (7) and H_1 receptors in guinea pig brain (86) that recall similar "mismatches" in other neurotransmitter systems (85, 300, 422). The increase in [3H]mepyramine binding in the developing rat brain parallels that of HDC, a presynaptic marker of HA neurons (134, 720, 756), as well as the HA-induced phosphoinositide hydrolysis (132). Whereas no change in cerebral H_1 -receptor density occurs after long-term inhibition of HA synthesis in adult mice (T. T. Quach and J. C. Schwartz, unpublished observations) in newborn rats, their density increases after chronic treatments with a H_1 -receptor antagonist (720) and decreases after treatment with an antithyroid agent (134).

3. Inositol phospholipid hydrolysis

The observation that responses mediated by H_1 receptors are Ca^{2+} dependent led to the proposition that this receptor subtype was linked to calcium mobilization (656). An early event associated with the stimulation of several calcium-mobilizing receptors is the hydrolysis of inositol phospholipids in the plasma membrane that occurs via activation of the enzyme phospholipase C and releases two types of intracellular messengers: inositol phosphates (inositol 1,4,5-trisphosphate and inositol 1,3,4,5-tetrakisphosphate), which mobilize Ca^{2+} , and 1,2-diacylglycerol, which activates the intracellular protein kinase C (66, 468, 508). Even before general acceptance of the phosphatidylinositol cycle as a major transduction mechanism, it was shown that intracisternal HA accelerates the incorporation of inorganic ^{32}P into inositol phospholipids (220) via H_1 -receptor stimulation (719). Meanwhile, mepyramine-sensitive stimulation of phosphatidylinositol turnover by HA was shown to occur in the guinea pig ileum (361). In a more direct study of the initial steps of the cycle, H_1 -receptor stimulation was shown to trigger the rapid accumulation of [3H]inositol 1-phosphate in brain slices incubated in the presence of [3H]inositol and Li^+ , an inhibitor of inositol 1-phosphatases (65, 97, 115, 116, 131, 158, 159, 173, 386, 831). Other inositol phosphates, i.e., inositol 1,4-bisphosphate and inositol 1,4,5-trisphosphate, are also rapidly accumulated under similar conditions (115, 173, 174). The amplitude of the phosphoinositide response is correlated with the H_1 -receptor density in regions of guinea pig brain (115, 158, 159) or during brain development in rats (720). Interestingly, in guinea pig cerebral cortex, the half-maximal concentrations of HA to trigger the phosphoinositide response and the inhibition of [3H]mepyramine are similar (115, 158, 159), and both parameters are similarly reduced by partial irreversible inactivation of H_1 receptors (131). This indicates that the response occurs without any significant receptor reserve, an observation consistent with this response

playing a primary role in signal transduction. However, this does not apply to the response in cerebellum on which the effects of partial agonists also suggest a different coupling efficiency (115, 173). The fact that the response to HA is markedly reduced by calcium chelators (115, 386) does not rule out that it is responsible for Ca^{2+} translocation, since this may only reflect the requirement of a minimal Ca^{2+} concentration for phospholipase C activity (353). In cultured vascular smooth muscle cells, H_1 -receptor stimulation elicits a transient increase in intracellular Ca^{2+} , which is presumably due to its intracellular mobilization, since it persists in the absence of extracellular Ca^{2+} (459). In contrast with a previous report (695a), H_1 -receptor stimulation was also found to increase intracellular Ca^{2+} in neuroblastoma cells, but the response was attributed mainly to the increased entry of extracellular Ca^{2+} and led to hyperpolarization via activation of K^+ channels (517, 518).

Adenosine, despite having no direct effect alone, potentiates the H_1 receptor-mediated hydrolysis of inositol phosphoinositides elicited by HA in guinea pig cerebral cortical slices (308, 309, 321). In contrast, adenosine (385) and GABA (146), which coexist in HA neurons, both inhibit the HA-induced response in slices of mouse and rat cerebral cortex, respectively. Excitatory amino acids also inhibit the HA-induced response in hippocampal slices (54).

4. Potentiation of adenosine 3',5'-cyclic monophosphate accumulation

Histamine is among the most powerful stimulants of cAMP accumulation in brain slices (153, 371), and this is attributable to the participation of both H_1 and H_2 receptors in this response (56, 169, 618). Whereas only H_2 receptors are directly linked to the cyclase and the increase in cAMP formation elicited by their activation can be observed in cell-free preparations (298), the effect mediated by H_1 receptors is an indirect one, consists of a large amplification of the cAMP response mediated by H_2 receptors (from a 2- to 3-fold to up to a 15-fold increase), and can be evidenced only in intact cell preparations, such as slices of guinea pig hippocampus conjointly stimulated by H_2 -receptor agonists (539). Both H_2 and H_1 receptors mediate the cAMP response to HA in low and high concentrations, respectively. A similar process was shown to operate in slices of rabbit cerebral cortex (8) as well as in vesicular entities (microsacs) of guinea pig cerebral cortex (154, 155, 587).

Stimulation by the H_1 receptor may amplify the cAMP response via one of the two signals known to be generated by the phosphatidylinositol cycle. However, although the H_1 receptor-mediated response is not modified through activation of protein kinase C by phorbol esters (238a), it is significantly reduced in the absence of Ca^{2+} (8, 238b, 661, 666), suggesting that the inositol phosphate branch of the cycle and the Ca^{2+} mobilization that it triggers play a major role. Intracellular Ca^{2+} may activate the adenylate cyclase via interaction with a cal-

modulin-calmodulin binding protein complex in the catalytic subunit of the enzyme.

In a parallel manner, stimulation of H_1 receptors amplifies the cAMP response generated in intact cell preparations by other direct activators of the cyclase, e.g., adenosine (160, 169, 172, 320, 321), catecholamines acting via α -adrenergic receptors (147, 154), or vasoactive intestinal peptide (VIP) (449). The involvement of the products of inositol phospholipid hydrolysis in the potentiation by H_1 -receptor agonists of the cAMP response to adenosine was also studied using phorbol esters and a calcium ionophore, but no clear conclusion could be drawn (157, 322, 323).

Baclofen and other GABA_B-receptor agonists potentiate the cAMP response induced in rat cortical slices by HA; however, the HA receptor subclass involved was not identified (380). Similar amplifications are found on stimulation of α_1 -adrenergic receptors, also linked with the phosphatidylinositol cycle (153, 449).

These amplification processes might be functionally important, inasmuch as they allow enlarged responses to a single transmitter in increasing concentrations as well as mutual potentiations of the responses triggered by two neurotransmitters, e.g., HA and norepinephrine, reaching simultaneously the same target cell. The potentiation between HA and adenosine might also be functionally important in view of a possible corelease of these substances from the same tuberomammillary cells.

5. Glycogenolysis

Although less abundant than in liver or muscle, glycogen represents in brain one of the major energy reserves (at least 25% of the total) and may therefore be vital for meeting the high energy expenditure of neuronal activity in the CNS. It is found not only in glial but also in neuronal cells (345). In brain the polysaccharide stores appear to be in a high dynamic state and to be controlled by several neurotransmitters (666). Cerebral glycogenolysis is studied *in vivo* in the neonatal chick, which lacks a blood-brain barrier (203, 479), or, more conveniently, on brain slices in which levels of [³H]glycogen (synthesized from [³H]glucose) are monitored using a simple assay (590, 595). Glycogenolysis is triggered by norepinephrine (203, 448, 480, 593, 595), histamine (590, 592, 595), adenosine (595), VIP (448), or 5-HT (594). The effect of these various agents is due to phosphorylase activation in the slice preparation (790), which may occur either via cAMP accumulation, e.g., for responses mediated by β -adrenergic (593, 595) or VIP receptors (448), or via translocation of Ca^{2+} , which may activate phosphorylase kinase by binding to its calmodulin subunit (135). The latter mechanism seems to apply to the glycogenolytic response to HA that requires Ca^{2+} in the external medium and is strictly mediated by H_1 receptors (590). An interesting feature of the HA response is that it apparently occurs in a manner similar to that mediated by β -adrenergic receptors (593) with a large receptor reserve (24, 590), which is consistent with the

large signal amplification provided by the glycogenolytic cascade. In addition, rapid, selective, and rather large desensitization of the HA response, accompanied by limited changes in [³H]mepyramine binding, can be observed in this system (592).

6. Guanosine 3',5'-cyclic monophosphate accumulation and other biochemical responses

Activation of guanylate cyclase and of inositol phospholipid hydrolysis appears to be a related cellular event (66, 318), which may explain why H_1 receptors mediate the HA-induced stimulation of guanosine 3',5'-cyclic monophosphate (cGMP) formation in mouse neuroblastoma cells (609, 611, 738). This response, similar to others mediated by H_1 receptors, requires an intact cell preparation and is Ca^{2+} dependent, suggesting that it is mediated by an increase in intracellular Ca^{2+} , but the latter could not be shown using the fluorescent probe aequorin (695a). In the same preparation, H_1 -receptor stimulation triggers arachidonic acid release, possibly via activation of phospholipase A_2 , which may indirectly be responsible for the cGMP response (695a). Stimulation of H_1 receptors in blocks of bovine sympathetic ganglia also increases cGMP accumulation (712). Finally, HA-induced cGMP responses were reported using brain slices (153, 425), but the responsible receptor subtype (presumably H_1) was not characterized. Histamine increases [³H]norepinephrine release from brain slices, apparently via H_1 -receptor stimulation (717). However, it increases endogenous norepinephrine release via a nonreceptor mechanism (836a).

7. Electrophysiological responses

Despite many studies of electrophysiological responses elicited by HA in CNS preparations (for reviews see Refs. 275, 276, 615), those mediated by H_1 receptors are generally not well defined, and their underlying membrane mechanism is poorly understood. One reason is that no highly selective H_1 -receptor agonist is available and that many H_1 -receptor antagonists have local anesthetic properties, which makes the interpretation of their effects often difficult. Nevertheless, it appears that iontophoretic application of HA to cerebral neurons often leads to excitatory responses when mediated by H_1 receptors. *In vivo*, osmosensitive neurons in cat supraoptic nucleus, also identified by antidromic invasion from the hypophyseal stalk, increase their firing rate when HA is applied, and this effect is blocked by mepyramine (281, 285). Whereas in cultured supraoptic nucleus neurons no effect of HA was observed (631), excitatory actions of HA, rather well characterized as being H_1 receptor mediated, were observed on acutely prepared explants of the same neurons (19). These excitations mainly occurred in cells either spontaneously active or in which burst activity had been induced antidromically, indicating that they were dependent on electrical activity expressed by the neurons. Although

the underlying membrane mechanism was not studied, it was suggested that HA influenced a voltage-gated conductance via Ca^{2+} translocation.

Other excitatory responses mediated by H_1 receptors occur on cultured tuberal hypothalamic neurons (244, 246) or on hippocampal slices in which slow depolarizations without conductance changes are observed; in addition, on the latter preparation, HA augments excitatory postsynaptic potentials (EPSP) in the CA1 and CA3 areas, presumably via a presynaptic effect (675, 676). In the suprachiasmatic nucleus of slices of rat hypothalamus, local activation of H_1 receptors (similar to that of α_1 -adrenergic receptors) inhibits the negative wave elicited by stimulation of the optic nerve (439). On astrocytes of cultured rat brain stem and spinal cord, H_1 -receptor stimulation mainly causes depolarizations (325). Excitatory actions of HA after iontophoresis to various brain areas were reported (112, 272, 281, 285, 608), but their possible mediation by H_1 receptors was not shown.

B. Histamine H_2 Receptors

1. Molecular properties

Until very recently a selective labeling of the H_2 receptor was not achieved because of the limited affinity of available ligands. For instance, the saturable binding of [^3H]cimetidine to cerebral membranes was assumed to occur at H_2 receptors (102, 164, 377, 384, 718), but neither the affinity of the tritiated ligand nor the potency of competing agents corresponds to that expected from biological responses mediated by H_2 receptors (613, 693, 800). Tritiated ranitidine (92), [^3H]impromidine (665), or [^3H]ICIA 5165 (500) also proved to be unsuitable.

The utilization of [^3H]HA itself as a ligand has led to complex and somewhat perplexing results. Tritiated histamine binds with high affinity, i.e., with a K_D of 2–10 nM depending on the conditions, to cerebral membranes (43, 149, 542, 663, 704–706, 814) and to gastric mucosal cells (50, 51). In early studies with cerebral membranes, the binding appeared to occur to receptors, as shown by 1) its sensitivity to guanylnucleotides, 2) its neuronal localization suggested by the effects of kainate lesions, 3) its marked regional heterogeneity, and 4) its localization to synaptosomal membranes (43, 542). However, whereas histaminic drugs were active as competing agents, their potencies did not correspond to those at either H_1 or H_2 receptors (or at H_3 receptors that were not yet identified at this time), and it was suggested that the binding occurred at one of the HA receptors in the desensitized state. More recently in an extensive study in which binding parameters were widely varied, several components were distinguished, among which was one characterized by potencies of agonists (but not antagonists) corresponding to those at H_2 receptors. It was proposed that the binding occurred to an allosteric site of the H_2 receptor, but this remains to be estab-

lished in functional studies (704–706). Whatever the site to which [^3H]HA binds, the ligand cannot be used to reliably label the H_2 receptor in biochemical or autoradiographic studies.

Although in several laboratories the antagonist [^3H]tiotidine had not been found suitable for labeling the H_2 receptor (49, 52, 442, 666), with the use of a more purified batch of the tritiated ligand, a fraction (~30–40%) of its binding to membranes of guinea pig brain (225, 364, 510, 612, 694, 711) or lung (217) apparently occurred to H_2 receptors, as judged from the potencies of antagonists. In contrast, the K_i values of HA and agonists were 10- to 100-fold higher than their half-maximal inhibitory concentration (IC_{50}) for biological responses mediated by H_2 receptors (including adenylate cyclase activation), implying that the latter occurs with a very large receptor reserve (225). Although significant binding could be detected in three brain areas (cerebral cortex, striatum, hippocampus), this was not the case for other areas or peripheral tissues known to contain H_2 receptors, presumably due to a high nonspecific binding.

More recently, [^{125}I]iodoaminopotentidine, a ^{125}I antagonist, was designed as a highly potent ($K_D = 0.3$ nM), sensitive, and selective ligand for H_2 receptors (624a, 754a). With this probe the nonspecific binding represented <20–30%, which allowed it to be used not only in biochemical but also in autoradiographic studies (456a, 624a). The corresponding azido derivative was designed as a photoaffinity probe for the H_2 receptor and was shown to bind irreversibly to 58- and 32-kDa peptides isolated by electrophoresis. The H_2 -receptor ligands prevented the labeling of these peptides, which were therefore identified as containing the HA recognition domain of the H_2 receptor (624a).

2. Adenylate cyclase activation

Several years before the definition of H_2 receptors and the design of selective antagonists, HA was shown to stimulate adenylate cyclase in broken cell preparations from guinea pig heart, and this effect was shown to be blocked by antihistamines in concentrations well above those required for interaction with H_1 receptors (398, 432, 465). As summarized (153, 487), in brain, most early studies were performed with slices in which the responses are much larger than in membranes, e.g., in rabbits (218, 371), guinea pigs (686), rats (653) or humans (409, 687), but they are more complex since, with the exception of the chick (481, 482), they do not involve a single receptor (see sect. VA4).

However, despite its limited stimulation (2- to 3-fold) on cell-free preparations from guinea pig hippocampus, a HA-sensitive adenylate cyclase could be characterized biochemically and pharmacologically as being selectively linked to the H_2 receptor (257, 298, 333, 379). Although rat brain adenylate cyclase is much less sensitive to HA than is guinea pig, some stimulation was reported (257, 298, 548, 580). In several peripheral

tissues, e.g., heart or stomach, where biological responses mediated by H_2 receptors occur, a HA-sensitive adenylate cyclase, also selectively linked to the H_2 receptor, was characterized (for review see Ref. 363). Furthermore, a number of H_2 receptor-mediated responses are mimicked by cAMP analogues and potentiated by phosphodiesterase inhibitors, suggesting that cAMP is the universal second messenger of HA at H_2 receptors.

The enzyme is activated by HA, which, in rather low concentration ($EC_{50} = 10 \mu M$), increases its maximal reaction velocity without altering the K_m for its substrate Mg-ATP. The nucleotide guanosine triphosphate stimulates the enzyme and markedly potentiates the HA-induced stimulation, indicating that the ternary model (617) comprised of the H_2 receptor (the HA recognition subunit), a GTP regulatory protein (G_s) (the transducer), and adenylate cyclase (the catalytic unit) applies to this system. Free Mg^{2+} stimulates the catalytic activity presumably by interacting with an allosteric site of the enzyme, the affinity of which might be increased on HA stimulation (379).

The adenylate cyclase response in membranes of guinea pig brain is triggered by H_2 -receptor agonists and competitively inhibited by typical H_2 -receptor antagonists at concentrations closely consistent with those required at H_2 receptors mediating various biological responses (257, 298). However, an intriguing observation is that a series of psychotropic compounds, namely several neuroleptics and a number of structurally diverse antidepressants, behave as extremely potent and competitive inhibitors of the response to HA on cerebral membranes (257, 259, 378). This has led to the suggestion that blockade of the H_2 receptor represents the molecular basis of clinical antidepressant activity (378). However, on intact cell preparations, i.e., hippocampal slices (156) or dissociated brain tissues (374), stimulated by selective H_2 -receptor agonists, these compounds are relatively weak antagonists. The reasons for these intriguing differences are not known, and stimulation of adenylate cyclase in membranes should not be regarded as a reliable system to assess the activity of compounds at H_2 receptors. In addition, the idea that antidepressants derive their clinical efficacy from blockade of cerebral H_2 receptors seems unlikely, particularly since such a blockade could not be observed after chronic treatments (514).

In several systems increased intracellular cAMP content leads to final biological responses via enhanced phosphorylation of intracellular proteins. However, although stimulation of H_2 receptors in gastric parietal cells was shown to selectively activate a cytosolic type I cAMP-dependent protein kinase (124) and to stimulate the phosphorylation of several cytosolic proteins (125, 451), the corresponding effects on cerebral H_2 receptors were not reported. These intracellular steps mediated by cAMP might be regulatory steps, because electrophysiologically hypersensitive responses to HA elicited by denervation (286) or chronic antidepressant treatments (514) are not accompanied by changes in responsiveness of the cAMP system to HA.

3. Phospholipid methylation and other biochemical responses

Hirata and Axelrod (316) suggested that methylation of membrane phospholipids plays a role in signal transduction across membranes. Stimulation of H_2 receptors in mast cell membranes (754) and synaptic membranes of rat brain (536, 537) rapidly increases incorporation of [3H]methyl groups from S -[3H]adenosylmethionine into phospholipids. On the latter preparation, the EC_{50} of HA was $5 \mu M$, and concentration-response curves obtained with several agonists and antagonists rather clearly identified the H_2 receptor as mediating the response. Although controversial (836a), release of endogenous norepinephrine might be modulated by H_2 receptors (79a). The absence of correlation between the density of binding sites and adenylate cyclase activity (624a) might reflect the existence of H_2 -receptor subtypes, possibly linked to these various responses.

4. Localization

Until recently the information on H_2 -receptor localization in the brain was essentially derived from studies of the cAMP response they mediate. The fact that this response occurs in neurons is suggested by several observations: 1) the HA-sensitive adenylate cyclase is enriched in synaptic membranes isolated from guinea pig cerebral cortex (379); 2) the cAMP response occurs on various fractions enriched in neuronal elements, e.g., the vesicular sacs called synaptoneuroosomes (229, 230, 322, 323, 548, 586, 587); and 3) kainate lesions in the hippocampus nearly abolish the response in slices (234), whereas interruption of HA afferents does not affect it (286). The prenatal development pattern of the cAMP response is also consistent with a neuronal localization of H_2 receptors (689).

The cAMP response involving H_2 receptors is not limited to neurons, since it can be also evidenced in human astrocytoma cells (129), epithelial cells of choroid plexus (148), and cerebral microvessel preparations (341, 367, 382, 546, 547). However, a clear cAMP response can only be measured in a few brain areas of a few animal species, and the amplitude of the response (153, 670) does not parallel the relative densities of histaminergic afferents, which suggests that mismatches exist for not only H_1 but also H_2 receptors.

In contrast with binding data obtained with [3H]tiotidine (612, 694), autoradiographic mapping of the H_2 receptor in guinea pig or rat brains using [^{125}I]aminopotentidine has shown it to be distributed widely and in a highly heterogeneous fashion, e.g., with clearcut differences among laminae of cortical areas, suggesting its major association with neurons (624a).

The H_2 receptors are present in most areas of the cerebral cortex, with the highest density in the superficial layers, the piriform and occipital cortex, which contain low H_1 -receptor density. The caudate putamen (which contains low H_1 -receptor density), nucleus accumbens, and olfactory tubercles are among the richest

brain areas. In the hippocampal formation, H_2 receptors display a laminated pattern with dense labeling in the lacunosum moleculare, radiatum, and oriens layers. In the thalamus the low density of H_2 receptors contrasts with the high density of H_1 receptors. The H_2 receptors are not abundant in the hypothalamus (where HA axons are the densest) nor in most other brain areas except the superficial gray layer of colliculus superior and, to a lesser extent, the substantia nigra. These distributions suggest that H_1 and H_2 receptors may mediate together the actions of HA in certain brain areas, e.g., cerebral cortex or hippocampus, whereas in other areas, e.g., thalamus or caudate putamen, a single subtype might be primarily involved. The H_2 receptors are hardly detectable in pituitary.

5. Electrophysiological responses

In early studies in which HA was applied by microiontophoresis on many neurons all over the CNS of anesthetized animals, the response most frequently found was an inhibition of firing, with both fast onset and fast recovery (for review see Refs. 276, 277). This pattern was found on neurons from the cerebral cortex (279, 285, 563, 564, 639), the brain stem reticular formation (89, 278), the dorsal raphe nucleus (427, 428), the cerebellum (458, 690), the vestibular nucleus (391, 641), the thalamus and hippocampus (273, 285), the ventromedial nucleus of the hypothalamus (608), and the preoptic area (112). These depressive actions may be mediated by H_2 receptors, as suggested in some of these studies by the blockade exerted by burimamide, metiamide, or cimetidine. However, this conclusion is only a tentative one, since 1) the iontophoretic application does not allow one to determine the apparent affinities of antagonists, 2) metiamide and even more burimamide are now known to display very significant H_3 -receptor antagonist potency, and 3) the highly selective H_2 -receptor agonists dimaprit and impromidine were generally not tested.

Iontophoretically applied metiamide also antagonizes, at least partly, the depressant responses of cerebral cortical neurons elicited by stimulation of the medial forebrain bundle, of hippocampal cortical neurons elicited by stimulation of the fornix (284, 285, 640), or of nucleus accumbens neurons evoked by stimulation of the afferent fimbria (126). These various data suggest that H_2 receptors mediate the inhibitions elicited by endogenous HA, a view supported by the clear hypersensitive inhibitory response that develops in the guinea pig sensorimotor cortex after lesions of the ascending HA pathway (286).

On unidentified cells of explants of tuberal hypothalamus, iontophoretic application of HA also elicits depressant effects with a rapid time course, which are clearly mediated by H_2 receptors; furthermore the persistence of the response in a Ca^{2+} -free medium and its potentiation by phosphodiesterase inhibitors suggest that it is postsynaptically mediated by an increase in cAMP (245, 246). Histamine hyperpolarizes human spi-

nal neurons in culture (588). A similar effect is mediated by H_2 receptors on astrocytes of cultured rat brain stem and spinal cord (326) and on suprachiasmatic neurons of rat hypothalamic slices (439).

In slices of rat hippocampus, local pressure or iontophoretic application of HA or impromidine to pyramidal or granule cells hyperpolarizes these cells via a presumably postsynaptic effect (273). Perhaps more important effects, apparently mediated by H_2 receptors, were evidenced on the same preparation by Haas and colleagues (274, 276, 280, 282, 283) when HA or impromidine was added to the perfusion fluid and when CA1 pyramidal neurons were recorded intracellularly. Histamine caused a slight depolarization without change in resting membrane conductance, an abbreviation of long afterhyperpolarizations, and a loss of accommodation of action potential firing to excitatory inputs. The two latter actions result in a strong potentiation by HA of various excitatory signals, e.g., depolarization induced by excitatory amino acids and synaptically evoked spikes, by inhibition of their self-restriction processes. These effects were attributed to a decrease of a Ca^{2+} -activated K^+ conductance (283), a mechanism confirmed by voltage-clamp studies (556) and that may also underlie the action of HA at medullary (90, 366) or myenteric neurons (490). A similar mechanism might be responsible for the H_2 receptor-mediated enhancement of excitability of CA3 pyramidal neurons treated with penicillin (523) or after stimulation of mossy fibers (729). These indirect excitatory effects might depend on intracellular cAMP inasmuch as they are potentiated by a phosphodiesterase inhibitor and mimicked by intracellular application of the nucleotide (275) or activation of the cell's adenylate cyclase by forskolin (499).

Abbreviation of afterhyperpolarization in the same cells triggered by stimulation of β_1 -adrenergic receptors also occurs via a similar mechanism (499). A similar effect elicited by stimulation of muscarinic receptors (59) might result from intracellular protein kinase C activation (39). Therefore it appears that inhibition of a Ca^{2+} -dependent K^+ conductance might represent the final common path for the actions of various neurotransmitters released from several highly divergent neuronal pathways. Hence, as underlined (276), these essentially modulatory actions of HA, consisting of a weak direct effect but a strong potentiation of excitatory signals, suggest that the function of the amine in brain is not to transmit discrete information but to regulate in a coordinate manner the excitability of large cerebral areas (655, 660).

C. Histamine H_3 Receptors

1. Molecular properties

The highly potent agonist R - α -[3H]methylhistamine (MeHA) constitutes a suitable probe for the selective labeling of the H_3 receptor (23). In the absence of divalent cations, R - α -[3H]MeHA binds in a saturable

manner to an apparently homogeneous population of sites in membranes of rat cerebral cortex. The binding is reversible, as indicated by the similar dissociation constants ($K_D = 0.3$ nM) derived from either association-dissociation kinetics or saturation kinetics at equilibrium ($K_D = 0.4$ nM). These binding sites are pharmacologically identified as H_3 receptors by competition studies performed with various H_1 , H_2 , or H_3 histaminergic drugs (28a). The relative potencies of various agonists and affinity constants of various antagonists are highly correlated with the corresponding values obtained at functional H_3 autoreceptors regulating HA release or synthesis. For instance, the *R*-isomer of α -MeHA is ~ 10 times as potent as HA itself, and *S*- α -MeHA is ~ 100 times less potent than *R*- α -MeHA. This confirms that enantiomers corresponding to *S*-configured L-histidine are highly preferred at H_3 receptors, whereas enantiomers corresponding to D-histidine are more potent at H_2 receptors, with no difference being observed at H_1 receptors (23, 29). The potent and specific H_3 -receptor antagonist thioperamide (23), the H_1 -receptor agonist betahistine (24), the H_2 -receptor agonist impromidine (25), and the psychoactive drug phencyclidine (21) inhibit *R*- α -[3 H]MeHA binding with the same affinity as that displayed when tested as antagonists at functional H_3 autoreceptors.

Two affinity states of the H_3 receptor are observed when the binding of *R*- α -[3 H]MeHA is studied in the presence of Ca^{2+} in physiological concentrations, an effect that is not reproduced by Mg^{2+} and apparently arises from the conversion of a major fraction of H_3 receptors to a lower affinity state ($K_D = 16$ nM). The binding of the tritiated ligand to this low-affinity component is entirely and specifically inhibited in the presence of guanylnucleotides, indicating that the H_3 receptor is coupled to its (so far unknown) effector system via a G protein. However, at numerous other receptor types, guanylnucleotides affect binding to the high- and not the low-affinity component (28a). The low-affinity component may correspond to the functionally active receptor, since the K_D value of *R*- α -MeHA at this component is close to its EC_{50} values at H_3 autoreceptors regulating HA release and synthesis. However, the functional involvement of the high-affinity population of sites cannot be entirely excluded, since it also appears to be (although very partially) GTP regulated. The 10 times higher affinity of agonists to this high-affinity component compared with their potency in functional studies suggests that these sites may represent the H_3 receptor in a modified (desensitized?) state.

2. Distribution in central nervous system

The mean density of cerebral *R*- α -[3 H]MeHA binding sites determined in physiological conditions in rats is rather low, i.e., ~ 30 fmol/mg membrane protein. It is slightly higher in the guinea pig brain, suggesting that the number of H_3 receptors, similar to that of H_1 receptors, varies among species. The H_3 receptors mediate the

autoinhibition of HA release in human brain with a pharmacology apparently similar to that of corresponding receptors in rodents (22).

The distribution of H_3 receptors in rat brain, established from either membrane binding studies or autoradiographic studies, is highly heterogeneous (23; H. Pollard, J. Moreau, J. M. Arrang, and J. C. Schwartz, unpublished observations; Fig. 2).

In cerebral cortex where they are rather dense, H_3 receptors are found in all areas and layers with, however, a higher abundance in rostral areas and in laminae IV and V. In the hippocampal formation, they are moderately to highly abundant, with their density being the highest in the dentate gyrus, moderate in subiculum, and very low in the fimbria. In the amygdaloid complex high densities are found in central, lateral, and basolateral nuclei as well as in the bed nucleus of the stria terminalis, which contains a dense histaminergic innervation (60).

In the basal forebrain, numerous H_3 receptors are present in anterior olfactory nuclei, nucleus accumbens, and olfactory tubercles, as well as in striatum, particularly in its dorsomedial part; they are less numerous in the globus pallidus and even less in the septum. In the thalamus, H_3 receptors are mainly detected in various midline, intralaminar, and lateral nuclei. In the hypothalamus, their moderate density contrasts with the high density of HA axons, but they are detectable at the level of the tuberomammillary nucleus where they may reside on perikarya or dendrites (28). In the mesencephalon, they are numerous in the substantia nigra, particularly in its pars reticulata, the ventral tegmental area, and superior colliculi. In cerebellum, low densities are present in all layers. In the brain stem, they are mainly present in pontine nuclei, around the fourth ventricle, in locus coeruleus, and in the dorsal tegmental nucleus. In the spinal cord, a low density is present mainly in external layers of the dorsal horn.

This distribution of H_3 receptors, not strictly parallel to that of histaminergic axons, suggests that they are not restricted to the latter. This is confirmed by the identification of H_3 receptors on serotonergic and noradrenergic nerve terminals in the cerebral cortex (652, 652a) and a cerebral vessel (197). Their decrease elicited in striatum by local administration of the neurotoxin kainate is consistent with a major neuronal localization (Pollard et al., unpublished observations).

In the vegetative nervous system, H_3 receptors with a presynaptic localization have been evidenced at the level of the mesenteric artery where they mediate inhibition of excitatory junction potentials generated by stimulation of sympathetic perivascular nerves (354). Also, their stimulation inhibits transmission at nicotinic synapses of enteric ganglia (737), an effect that may be responsible for the inhibition of electrically evoked contractions of the ileum (762). Presynaptic H_3 receptors on vagal nerve endings might also be responsible for the inhibition of cholinergic transmission in airways (348a, 349) and of gastric acid secretion (301, 302). Presynaptic H_3 receptors might also mediate inhibition of neuropep-

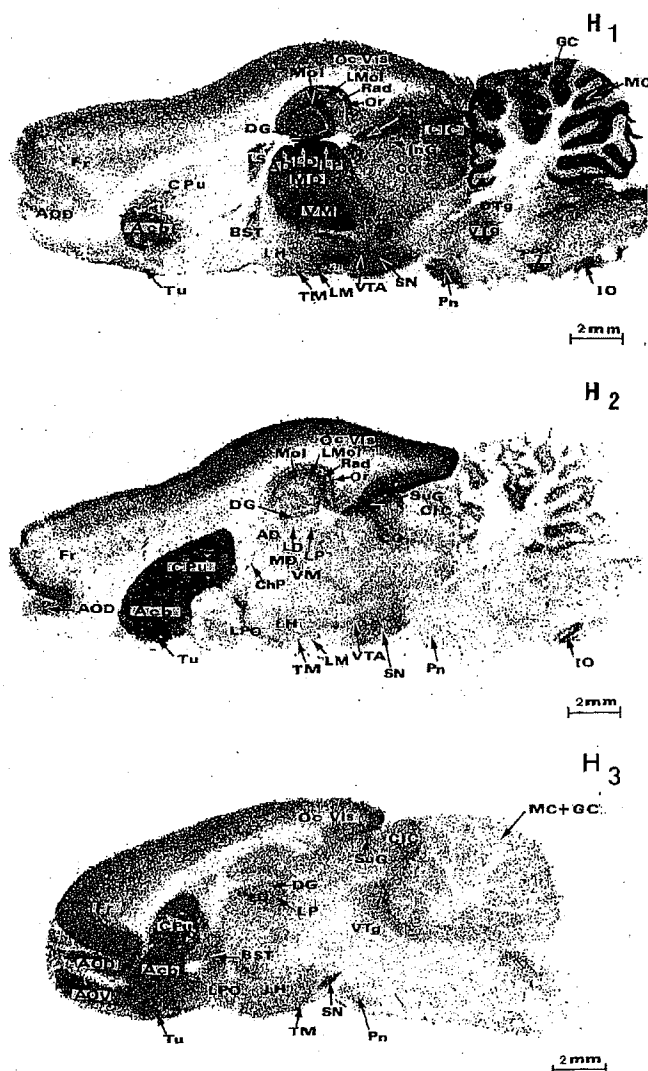


FIG. 2. Autoradiographic localization of histamine receptors on midsagittal sections of brain. H_1 and H_2 receptors were visualized on sections of guinea pig brain using [125 I]iodobolpyramine and [125 I]iodoaminopotentidine, respectively. (Courtesy of M. L. Bouthenet.) H_3 receptors were visualized on section of rat brain using R - α -[3 H]methylhistamine. Abbreviations: ACb, nucleus accumbens; AD, anterodorsal thalamic nucleus; AOD, anterior olfactory nucleus, dorsal part; AOV, anterior olfactory nucleus, ventral part; BST, bed nucleus of stria terminalis; CIC, central nucleus of inferior colliculus; CG, central gray; ChP, choroid plexuses; CPu, caudate putamen; DG, dentate gyrus; DTg, dorsal tegmental nucleus; Fr, frontal cortex; GC, granular layer of cerebellum; InG, intermediate gray layer of superior colliculus; IO, inferior olive; LD, laterodorsal thalamic nucleus; LH, lateral hypothalamic area; LM, lateral mammillary nucleus; LMol, lacunosum molecular layer of hippocampus; LP, lateral posterior thalamic nucleus; LPO, lateral preoptic area; LS, lateral septum; MC, molecular layer of cerebellum; MD, mediodorsal thalamic nucleus; Mol, molecular layer of hippocampus; Oc Vis, occipital visual cortex; Or, oriens layer of hippocampus; Pn, pontine nuclei; Rad, stratum radiatum of hippocampus; SN, substantia nigra; SuG, superficial gray layer of superior colliculus; TM, tuberomammillary nucleus; Tu, olfactory tubercle; VM, ventromedial thalamic nucleus; VTA, ventral tegmental area; VTg, ventral tegmental nucleus; 7, 7th cranial nerve.

tide release from airway sensory nerves (348b, 348c). Hence H_3 receptors are not restricted to the brain.

3. Actions mediated by H_3 receptors

The best established actions mediated by H_3 receptors are the presynaptic inhibitions of release of several neurotransmitters, i.e., HA, 5-HT, and norepinephrine in the brain and possibly acetylcholine, norepinephrine, and neuropeptides in the peripheral nervous system. As in the case of other presynaptic receptors, these actions may arise from a restriction of Ca^{2+} influx related to increases in hyperpolarizing conductances, possibly mediated by changes in channel phosphorylations resulting from inhibition of adenylate cyclase (511).

Stimulation of H_3 receptors decreases wakefulness in cats (369, 437a) and spontaneous motor activity in rats (93). It induces vasodilation of the rabbit isolated middle cerebral artery (197).

Nonneuronal (mast cell?) H_3 receptors mediate the inhibition of HA synthesis in various peripheral tissues (23).

VI. ROLE OF HISTAMINERGIC NEURONS IN NEUROENDOCRINE CONTROLS

Both the morphology of HA perikarya, recalling that of magnocellular secretory neurons in the anterior hypothalamus, and the high density of their projections to hypothalamic areas involved in the regulation of hormonal secretions are consistent with a participation of endogenous HA in neuroendocrine controls. In agreement with this hypothesis, exogenous HA elicits a variety of hormonal responses *in vitro* or *in vivo*, but the role of endogenous HA has been difficult to demonstrate (for reviews see Refs. 178, 179, 770, 810).

Systemic administration of HA elicits marked biological responses, such as hypotension or adrenal hormone secretion, which in turn may indirectly affect neuroendocrine controls. Because such changes may not involve histaminergic systems in the brain, they are generally not considered here.

A. Posterior Pituitary Hormone Secretion

Both the supraoptic and paraventricular nuclei of the hypothalamus, which synthesize and control the release of vasopressin and oxytocin, contain high levels of HA (98) and HDC activity (567) and high densities of HA axons (551). The neurohypophysis itself contains, mainly in its peripheral part, HDC- and HA-immunoreactive fibers, presumably arising from the TM and passing through the internal layers of the median eminence and the infundibular stalk (351). The H_1 receptors are extremely abundant in the supraoptic nucleus and present in the paraventricular nucleus (86, 543).

In several animal species, intracerebroventricular administration of HA elicits antidiuretic responses (61,

69, 71, 317, 431, 772, 773), which seem to result from increased vasopressin secretion (69, 71, 171, 775, 776). The effects of various agonists and antagonists indicate that this action is selectively mediated by H_1 receptors (61, 317, 776).

Iontophoretic application of HA to the supraoptic nucleus increases the firing of the neurosecretory cells also via H_1 receptors, but the possibility of a distal effect was raised (285), and no effects were observed by others (45, 631). In perfused rat hypothalamoneurohypophyseal explants, HA excited and facilitated the burst activity of antidromically stimulated supraoptic neurons; the effects occurred via H_1 receptors and appeared to depend on the electrical activity of the neuron, suggesting that HA affected a voltage-dependent conductance (19).

Although the effects of exogenous HA seem well established, this is not the case for a possible participation of the endogenous amine in the control of vasopressin release. In Brattleboro rats genetically lacking vasopressin, the HA levels are elevated in several hypothalamic nuclei, including the supraoptic nucleus, and decreased in the neurohypophysis, but the functional significance of these findings is obscure (139). Pituitary vasopressin depletion induced by repeated administrations of hypertonic saline was accompanied by a significant decrease in HA levels in neurohypophysis (785), suggesting that the control of vasopressin secretion by HA might occur at the level of both perikarya and terminals of the neurosecretory neurons. Increased hypothalamic HA, induced by chronic His loads in rats, decreased vasopressin levels in the anterior hypothalamus but did not modify the hormone level in plasma; chronic inhibition of HA synthesis by α -FMH impaired the vasopressin response to adrenalectomy but did not modify significantly vasopressin secretion in controls (107). Hence HA neurons might control vasopressin secretion under certain circumstances, but since changes in basal secretion do not occur after HA depletion and were never reported after administration of H_1 -receptor antagonists alone, endogenous HA may not exert a tonic influence on neurosecretion under basal conditions.

The secretion of oxytocin is also enhanced after intracerebroventricular administration of HA, but high doses are necessary (171).

B. Prolactin Secretion

Secretion of this hormone by the lactotrophs of the adenohypophysis is mainly controlled, in a tonic inhibitory fashion, by dopamine released from tuberoinfundibular neurons into the median eminence capillaries of the portal system. There are various indications that HA might be involved in the control of prolactin secretion.

Intracerebroventricular administration of HA in male or ovariectomized estradiol-primed rats increases the plasma levels of prolactin (18, 176, 180, 184, 435, 614). Intravenous HA elicits similar responses in steroid-primed rats (614), in rhesus monkeys (193), and in hu-

man males (400, 406, 578). This effect does not appear to be exerted at the level of the anterior pituitary, because it is not observed after local injections or applications of HA (435, 614). The anterior pituitary does not contain irHA axons (351), and H_1 or H_2 receptors appear scarce (M. L. Bouthenet, unpublished observations).

Histamine may act on central structures in the vicinity of the third ventricle, because the threshold doses of the amine are lower when given in the ventricle than in the lateral ventricle or systemically (178) and because prolactin secretion is also elicited by HA administered into the anterior hypothalamic area or the arcuate nucleus region (13, 15, 435). Histamine infused centrally decreases the secretion of dopamine into the pituitary portal blood of female (248) and male rats (404, 405). Dopamine receptor blockade by pimozide did not prevent the rise in plasma prolactin elicited by intracerebroventricular administration of HA (404). Hence the prolactin-stimulating effect of HA might occur through an inhibition of the tuberoinfundibular dopaminergic neurons. Both the arcuate nucleus and the median eminence contain irHA and irHDC axons (351) and H_1 receptors in moderate density (86, 543, 681). Receptor antagonists for 5-HT partially prevent the action of HA, suggesting a participation of the endogenous indolamine (405). The rat median eminence, which is located outside the blood-brain barrier, also contains mast cells depletable by compound 48/80 (567), and injection of this compound systemically, but not intraventricularly, increases prolactin secretion (182).

The receptor subtypes mediating the effect of HA have been subject to some controversy (for detailed discussion see Refs. 177, 178). The rise in prolactin secretion elicited by HA in rats is blocked by various H_2 -receptor antagonists injected intracerebroventricularly (183, 185, 186, 400, 402, 403) and mimicked by dimaprit, a selective H_2 -receptor agonist (186, 401). However, dimaprit was also shown to reduce plasma prolactin (186, 209). Intra-arterial administration of cimetidine or ranitidine, two H_2 antagonists that do not cross easily the blood-brain barrier, partially blocked the effect of intracerebroventricularly administered HA (403).

A possible participation of H_1 receptors in the HA-induced secretion of prolactin is less clear than that of H_2 receptors. The H_1 -receptor antagonists, such as mepyramine, that easily cross the blood-brain barrier (591) partially block the effect of centrally administered HA when they are administered intracerebroventricularly in relatively high dosages (180, 403) but do not block it when administered intravenously (405). Hence a nonspecific effect of the H_1 -receptor antagonists administered centrally, e.g., via membrane stabilization, seems likely. In contrast, systemically administered H_1 antagonists appear to block the prolactin secretion induced by intravenous HA, but the latter effect might be indirect and not mediated by cerebral receptors (406, 443, 614).

A possible role of endogenous HA in the control of prolactin release under various circumstances was investigated using receptor antagonists or a synthesis in-

hibitor as pharmacological tools. The H_1 -receptor antagonists administered systemically do not modify basal prolactin secretion in male rats (403) or in humans (406). In contrast, the H_2 -receptor antagonist cimetidine, given intravenously, promotes prolactin secretion in humans (104, 114, 406) or in rats (492), and chronic treatments with the drug produces gynecomastia and galactorrhea accompanied by hyperprolactinemia in a few patients (48, 163). These observations would not be consistent with a role of HA in promoting prolactin secretion via H_2 -receptor stimulation, but other observations suggest that the effect of cimetidine is not related to H_2 -receptor blockade. Hence the effect of cimetidine was not modified by the H_2 agonist impromidine (681); in addition, ranitidine was less effective than cimetidine, although it is a more potent H_2 antagonist, and oxmetidine, another H_2 antagonist, seems completely ineffective (407, 492, 683). Finally, a compound resembling cimetidine in chemical structure but devoid of H_2 -antagonist activity stimulated prolactin secretion (402). Because most H_2 antagonists do not easily cross the blood-brain barrier, it will be of interest to assess the action of the brain-penetrating antagonist zolantidine (108).

Depletion of hypothalamic HA by α -FMH (235) is accompanied by a decrease in basal plasma prolactin levels (495).

The rises in plasma prolactin elicited in male rats by restraint stress or acute exposure to ether vapors is prevented by several H_2 antagonists administered intracerebroventricularly as well as by α -FMH (12, 403, 495, 678). The H_1 antagonists administered systemically partially decrease the prolactin responses (12, 403). In contrast, the prolactin response triggered by suckling of lactating rats or by estrogens is blunted by H_1 antagonists but is not affected by H_2 antagonists (13, 18).

Taken together and despite several inconsistencies, these various studies suggest that cerebral histaminergic neurons participate in the control of prolactin secretion with a major involvement of H_2 receptors, but the participation of H_3 receptors remains to be assessed.

C. Thyrotropin Secretion

Thyrotropin (TSH) secretion by the adenohypophysis is controlled in a stimulatory fashion by thyrotropin-releasing hormone (TRH), a tripeptide released by neurons originating from the paraventricular and periventricular nuclei of the hypothalamus and ending in the external zone of the median eminence in apposition with the capillaries of the portal system. On the contrary, somatostatin, released at the same level from neurons originating from the periventricular area, inhibits TSH secretion.

Histamine might be involved in control of TSH secretion (for review see Ref. 765).

Intracerebroventricular administration of HA does not change basal TSH secretion (319, 443, 768) but decreases TSH secretion induced by either exogenous TRH (768) or by a cold stress (764, 766, 768, 769). Further-

more, His, in doses large enough to increase cerebral HA (668), inhibits the cold-stimulated (but not the TRH induced) TSH response, suggesting a role for endogenous HA (769). From the effects of focal injections, HA appears to act at the level of the periventricular hypothalamus (768) and not of the pituitary, since the amine did not modify basal or TRH-stimulated release of TSH from superfused rat anterior pituitary cells (767) and since dimaprit did not modify TSH release from anterior pituitary halves in vitro (167). The inhibition of the cold response by HA cannot be ascribed to an impaired release of TRH, since the amine actually liberates TRH from hypothalamic slices (123, 368) or synaptosomes (62), with both effects being apparently mediated by H_2 receptors. Theoretically the action of HA might result from somatostatin release, but this effect is not substantiated by experimental evidence. It is not clear whether the effect of HA on the cold response is receptor mediated since it was mimicked by impromidine or 2-pyridylethylamine but not antagonized by either mepyramine or cimetidine (768, 769). In contrast, systemic administration of the selective H_2 agonist dimaprit reduced serum TSH basal level in a cimetidine-reversible manner (167).

Furthermore, mepyramine and cimetidine administered alone do not modify the cold-induced secretion of TSH (768), suggesting that endogenous HA is not involved.

D. Growth Hormone Secretion

Growth hormone (GH) secretion is controlled in opposite fashions by GH-releasing factor (GRF) and somatostatin.

In unanesthetized male rats, intracerebroventricular administration of HA suppresses the spontaneous pulses of GH secretion, and this effect is partially mimicked by an inhibitor of HMT (491). This effect was not observed in rats in which most of the somatostatinergic innervation of the median eminence was eliminated (372), which may suggest that HA triggers somatostatin release. However, a somatostatin antiserum did not prevent the suppression of GH pulses by HA (493).

In anesthetized dogs, intracerebroventricular HA reduces GH secretion only slightly (625). In rats, HA also diminishes the GH secretion elicited by morphine, an action apparently mediated by H_1 receptors (494). Intracerebroventricular administration of GRF in low dosage elicits significant increases in HA concentrations in rat hypothalamus and pituitary, whereas somatostatin elicits opposite changes (106). These observations suggest reciprocal interactions between somatotropinergic and histaminergic systems in brain, but their relevance to the regulation of GH secretion remains to be clarified.

E. Adrenocorticotrophic Hormone Secretion

For a long time, a role for HA in the control of adrenocorticotrophic hormone (ACTH) secretion has

been postulated from the numerous observations showing that, on systemic administration, it elicits increases in plasma ACTH and corticosterone levels mainly via stimulation of H_1 receptors (178, 770, 810). In addition, various stressful procedures affect HA turnover in brain (see sect. XIII A). However, a participation of cerebral histaminergic neurons in the control of ACTH secretion largely remains to be clarified, since stimulation of peripheral H_1 receptors causes hypotension, a strong stimulus for ACTH secretion.

Intracerebroventricular administration of HA in doses low enough to avoid stimulation of peripheral receptors increases ACTH and/or corticosteroids secretion in both dogs (625) and rats (99, 101, 677) in which it is accompanied by an increased secretion of β -endorphin (399). In rats, H_1 receptors alone (677) or together with H_2 receptors seem involved (99, 101), whereas in dogs 4-methylhistamine, a predominantly H_2 -receptor agonist, decreases ACTH secretion (625). The action of HA does not appear to result from a direct secretory effect on either corticotropin hormone-releasing hormone (210, 314) or ACTH (630), as indicated by *in vitro* studies with hypothalamic and pituitary tissues, respectively. Hence an indirect action through other monoamines controlling ACTH secretion has been suggested (100, 600). However, iontophoretically applied HA strongly excites cortisol-inhibitable neurons in the mediobasal hypothalamus (452).

Controversial data have been obtained regarding the involvement of endogenous HA in the regulation of ACTH and corticosteroid secretion.

In rats neither H_1 nor H_2 antagonists prevent the ACTH and corticosterone responses elicited by an acute restraint stress (678) and, in mice, neither His loads nor inhibition of HA synthesis by brocresine, a nonspecific decarboxylase inhibitor, modifies the corticosterone response to restraint (789). In contrast, histidine loading raises plasma corticosterone levels in rats (462). Specific inhibition of HDC by α -FMH decreases plasma corticosterone in nonstressed as well as in stressed rats; however, because this effect is not accompanied by any significant change in plasma ACTH, a direct action of the inhibitor at the adrenal level was suggested (678).

In contrast, in humans the H_1 antagonist meclizine prevents the ACTH response to hypoglycemia or metyrapone, a corticosteroid synthesis inhibitor (9). In addition, in rats treated with α -FMH the ACTH response to adrenalectomy is completely abolished (793).

F. Gonadotropin Secretion

Secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are under the control of gonadotropin-releasing hormone (GnRH), and the secretion of both the pituitary and hypothalamic hormones is modulated by gonadal steroids.

Intracerebroventricular administration of HA in large doses evokes ovulation in anesthetized rabbits (644) and LH release in ovariectomized rats primed with estrogen and progesterone (176, 184, 435) but not in male

rats (181). This effect does not result from a direct stimulation at the pituitary level, since, *in vitro*, HA does not affect LH release from rat pituitary isolated cells (72) or fragments (123, 470). On the other hand, HA elicited GnRH release from perfused rat mediobasal hypothalamus, and GnRH was able to stimulate LH release from pituitaries sequentially perfused in a second perfusion chamber (470). The effect of HA could be mediated by H_1 receptors, since it was mimicked by 2-methylhistamine but not by 4-methylhistamine, two relatively selective agonists at H_1 and H_2 receptors, respectively, and antagonized by mepyramine, with the latter used, however, in high concentration (10 μ M). Although not directly assessed, a possible involvement of endogenous HA in the control of LH release is suggested by the observation that castration increases HA level in the hypothalamus of male rats (529) and HDC activity in the hypothalamus of female rabbits (76) and that brain HA levels fluctuate in the hamster during the estrus cycle and on selected days of pregnancy (315).

VII. ROLE OF HISTAMINERGIC NEURONS IN CARDIOVASCULAR REGULATION

In conscious or anesthetized animals, i.e., rats, cats, or goats, intracerebroventricular administration of HA increases blood pressure accompanied by bradycardia in conscious animals or tachycardia in anesthetized animals (162, 214-216, 241, 396, 397, 453, 581, 691, 761, 775, 819). These effects are not attributable to leakage of HA into the general circulation, because the amine has an hypotensive action when administered peripherally.

The central hypertensive action of HA results only partially from an activation of sympathetic activity, a participation of endogenous vasopressin being suggested by the attenuation of the response observed with a vasopressin antagonist (241). Cerebral catecholaminergic pathways may also contribute to this action, which is reduced after intracerebroventricular administration of the neurotoxin 6-hydrodopamine (214). The hypertensive response to HA might involve both H_1 and H_2 receptors, as suggested by the action of various agonists, including the highly selective agonist impromidine, but the effects of antagonists, often used intracerebroventricularly in extremely large doses, has led to contradictory results (214-216, 303, 453, 538, 581). In contrast to the above effects, HA administered into the C_1 area of the rostral ventrolateral medulla causes hypotension and bradycardia selectively via stimulation of H_2 receptors (253). In cats, HA perfused at high concentration enhances the pressor effect of stimulation of the caudal hypothalamus selectively via H_2 receptors (562).

Endogenous HA might have a role in central cardiovascular regulation. The spontaneous release of HA in superfusates of cat posterior hypothalamus seems to be altered according to modifications of blood pressure (560, 561). In two studies (138, 582), spontaneously hypertensive rats displayed increased HA levels in several hypothalamic areas, e.g., suprachiasmatic or arcuate nucleus and median eminence, but not in various brain

stem areas, whereas others failed to detect any difference (118, 740). In these hypertensive rats, the rate of basal HA release in superfusates of the posterior hypothalamus is significantly increased (779). Elevated brain HA levels induced by an inhibitor of HMT were accompanied by increased blood pressure and bradycardia, but blockade of this response by HA antagonists was not reported (396). In fact, the effects of HA antagonists given alone do not clarify the issue of a possible role of endogenous HA. Whereas most H_1 antagonists crossing the blood-brain barrier display little cardiovascular activity (188), H_2 antagonists administered intracerebroventricularly elicit biphasic or even hypertensive effects similar to HA itself (215, 242, 397). This paradoxical effect might be related to blockade of either brain stem H_2 receptors mediating hypotensive actions (253) or H_3 autoreceptors controlling HA release for which several H_2 antagonists display significant affinity (25).

VIII. ROLE OF HISTAMINERGIC NEURONS IN CONTROL OF CEREBRAL CIRCULATION

A possible role of HA in the control of cerebral circulation is suggested by the presence of mast cells (see sect. IIA) as well as of HA axons in vicinity of cerebral blood vessels (710). In addition, cerebral microvessels isolated by a sieving procedure contain measurable amounts of HA associated with HDC activity at a very low level (362, 381, 382) as well as H_1 receptors detected by [3H]mepyramine binding (557) and H_2 receptors mediating a cAMP response (38, 381, 382).

Histamine has multiple actions on cerebral blood vessels (for review see Refs. 262, 263, 534, 535).

On pial arteries and arterioles, perivascular microinjection of the amine elicits dilation mainly via activation of H_2 receptors, whereas pial veins and venules seem unresponsive (200, 264, 266, 794). The HA-induced dilation of pial arterioles of newborn pigs seems to be due to a production of vasodilator prostanoids (469).

On precontracted isolated preparations of cat (200, 201, 264) or rabbit middle cerebral arteries (680), HA produces vasodilation apparently mediated by H_2 receptors. This response seems to involve the endothelium, and at higher concentrations vasoconstriction mediated by H_1 receptors is observed. On precontracted human cerebral arteries, dilation involves H_1 and, to a lesser extent, H_2 receptors (532). In the rabbit precontracted preparation in which H_1 and H_2 receptors were blocked, HA in low concentrations still elicited vasodilation via activation of H_3 receptors, and this effect is mimicked by the selective H_3 agonist α -MeHA in extremely low concentration (197). In rats, extraluminally administered HA causes dilation of the spontaneous tone of isolated intracerebral arterioles via activation of H_2 receptors (150).

Intracarotid injection of HA in rats increases cerebral blood flow via activation of both H_1 and H_2 receptors but only after transient disruption of the blood-brain barrier by hypertonic urea (261, 265, 267). This may reflect the fact that the cerebral vessels are more

responsive to the amine when the latter is delivered to their external layers (534). In the human brain, however, transient vasodilative responses are observed, even when the blood-brain barrier is intact (750).

Histamine infused into rat internal carotid artery increases, via H_2 -receptor stimulation, the extravascular space for sucrose or horseradish peroxidase as well as the cerebral water content; electron-microscopic studies showed pericapillary astroglial processes to be swollen, consistent with cerebral edema (84, 196, 267). Blockade of H_2 receptors by ranitidine partially prevented the kainic acid-induced formation of brain edema, which preferentially occurs in the thalamus (728). In contrast, blockade of H_1 receptors by mepyramine in reasonable dosage did not modify significantly regional cerebral glucose utilization in conscious rats (267).

IX. ROLE OF HISTAMINERGIC NEURONS IN THERMOREGULATION

Several data suggest that HA participates in central temperature regulation. A dose-related hypothermia is observed after either intracerebroventricular injection of the amine (130, 684) or its local application to the rostral hypothalamus (91), a site where some thermoresponsive neurons are also depressed by iontophoretic application of HA (726). The effect of intracerebroventricular HA is potentiated by pretreatment with amodiaquin, an inhibitor of HA methylation (141). *tele*-Methylhistamine, the main HA catabolite in brain, is ineffective when given intracerebroventricularly (141, 441). Loading mice with His in doses able to double brain HA level has no effect on temperature (140), but a similar treatment induces a fall in core temperature of rats (260), and this response is suppressed by blockade of HA synthesis (144). Burimamide, metiamide, or cimetidine, when centrally administered, antagonizes the hypothermia induced by His, 4-methylhistamine, dimaprit, or impromidine (143, 260, 515, 566). These data strongly suggest that H_2 receptors in brain mediate the hypothermic action of HA.

On the other hand, the hypothermia produced by the local application of HA into the hypothalamus was also prevented by a systemic injection of an H_1 -receptor antagonist (91). Biphasic changes in the body temperature have been reported in cats after intracerebroventricular administration of HA (130). The immediate fall in temperature is followed by a slight hyperthermia occurring over a number of hours after the injection. Whereas mepyramine, a H_1 antagonist, blocks the HA-induced hypothermia, the delayed hyperthermia, which is mimicked by 4-methylhistamine, is suppressed by pretreatment with metiamide (130). To reconcile these findings it has been suggested (145) that HA affects the central thermoregulatory pathways by at least two mechanisms: stimulation of H_1 receptors located in the rostral hypothalamic thermoregulatory centers may lower the thermoregulatory set point, and stimulation of H_2 receptors, located elsewhere, may somehow activate efferent heat loss pathways directly.

The involvement of histaminergic systems in the thermal response to phencyclidine has also been proposed more recently (358). However, in anesthetized rats, stimulation of H_2 receptors in the nucleus preopticus medialis elicits a rise in core temperature (137).

Ionizing radiations in guinea pigs induce hypothermia, an effect mediated by both H_1 and H_2 receptors (376). Inhibition of HA synthesis by α -FMH did not modify body temperature in rats (83).

X. ROLE OF HISTAMINERGIC NEURONS IN EMESIS AND MOTION SICKNESS

Emesis is observed in dogs receiving HA intracerebroventricularly in high dosages, and the response is prevented by surgical ablation of the chemoreceptor trigger zone or by administration of H_1 - and H_2 -receptor antagonists (69, 70). The area postrema contains rather high levels of HDC activity in humans (657) and H_1 receptors in rodents (86, 414, 543).

Several H_1 antagonists are currently used to prevent motion sickness in humans, but their efficacy may derive from an associated antimuscarinic activity (188). Nevertheless, a possible role of endogenous HA is suggested by the presence of HA terminals and H_1 receptors in brain stem nuclei, such as the nucleus of the solitary tract or vestibular nuclei (7, 86) known to be involved in motion sickness.

On a behavioral model of motion sickness in rats, i.e., kaolin intake elicited by rotation, α -FMH had a beneficial effect; in addition, rotation induced a rise in brain stem HA that was prevented by labyrinthectomy (736).

XI. ROLE OF HISTAMINERGIC NEURONS IN CONTROL OF NOCICEPTIVE RESPONSES

A possible role of histaminergic neurons in the CNS in the control of pain has been recently reviewed (328, 626, 627).

Histamine administered intracerebroventricularly in rats (249) or mice (128, 526) impairs several nociceptive responses, e.g., in the writhing or hot plate jump tests, apparently via activation of H_2 receptors. A similar response is also observed after injections of HA onto neurons of the dorsal raphe (249) that are depressed (428); however, in contrast, this response apparently involves H_2 receptors. A control of pain perception by HA neurons would be consistent with their projections to and the presence of H_1 (86) and H_2 receptors (624a; M. L. Bouthenet, J. C. Schwartz, and M. Ruat, unpublished observations) in areas, e.g., the external plexiform layers of the dorsal horn of the spinal cord and mesencephalic periventricular grey matter, known to be involved in nociceptive controls (67). However, the numerous studies on the effects on H_1 -receptor antagonists administered alone do not clarify this issue (627). Several (but not all) compounds of this class display, like HA itself, antinociceptive activity in some tests involving supraspinal loci, whereas they are consistently ineffective in the tail flick response considered to be mainly controlled at the spi-

nal level. In addition, many of these compounds block not only H_1 receptors but also muscarinic or serotonergic receptors and the monoamine uptake systems. The fact that both the H_2 agonists and antagonists in high dosages (intracerebroventricularly) elicit antinociceptive responses does not clarify the issue. Thioperamide, a H_3 antagonist, does not modify a variety of nociceptive responses in mice (J. Costentin, personal communication).

A role of brain HA in a form of stress-induced antinociception has been postulated from the inhibition produced by the HDC inhibitor α -FMH or the H_1 -antagonist diphenhydramine, whereas cimetidine was ineffective (434). However, others found cimetidine and other H_2 antagonists including zolantidine, a brain-penetrating compound, effective, whereas the H_1 antagonist chlorpheniramine was not (250, 328, 331).

Morphine does not affect HA or *t*-MeHA levels (340, 504) but increases HA turnover in mouse brain (504). However, a role of brain HA in morphine analgesia was not substantiated by the effects of receptor antagonists and a HDC inhibitor (340).

XII. ROLE OF HISTAMINERGIC NEURONS IN CONTROL OF VIGILANCE, SLEEP, AND WAKEFULNESS

A large body of experimental evidence now supports the hypothesis (577, 655) that histaminergic neuronal systems in mammalian brain play an important role in arousal.

Intracerebroventricular administration of HA causes electroencephalogram desynchronization in rabbits, and this action is antagonized by mepyramine (471, 824). Intracerebroventricular administration of 2-thiazolyethylamine, a relatively specific H_1 agonist but not that of dimaprit, a H_2 agonist, increases wakefulness at the expense of slow wave and paradoxical sleep in rats (polygraphic recordings), and this effect is antagonized by systemic mepyramine in low dosage (472). Histamine injected into the ventrolateral posterior hypothalamus elicits a similar effect in cats, which is also antagonized by mepyramine administered locally or systemically in low dosage (436, 437). In this last study it was verified that sodium nitrite, a potent vasodilator, has no similar effect, suggesting that the action of HA is not indirectly due to its local vascular effects. These clear-cut data indicate that stimulation of H_1 receptors in this area where they were visualized by autoradiography (86) mediates arousal in various mammals. Because H_1 receptors do not appear to control either HA synthesis and release in vitro (25, 28) or the activity of histaminergic neurons in vivo (239, 570) and because short HA axons were visualized in this area (7), it appears that this arousal results from stimulation of postsynaptic H_1 receptors.

Various experimental approaches have also consistently shown that histaminergic neurons are involved in arousal mechanisms. In cats inhibition of HA synthesis by intraperitoneal α -FMH significantly increases deep slow-wave sleep and decreases wakefulness without modifying light slow-wave sleep and paradoxical sleep;

the drug has a similar effect when injected into the ventrolateral posterior hypothalamus (436, 437). The inhibitor administered systemically to rats has essentially similar effects; however, although in one study it was shown to occur during the "dark" phase (395, 793), in another study it mainly occurred during the "light" phase (473).

Conversely, inhibition of HA degradation via local injection of a HMT inhibitor to the ventrolateral posterior hypothalamus selectively increases wakefulness in cats (436, 437).

Arousal is also observed in cats after systemic administration of thioperamide, a H_3 antagonist, and to be blocked by administration of either *R*- α -MeHA, a H_3 agonist, or mepyramine, a H_1 -receptor antagonist (437a). These effects suggest that modulation of endogenous HA release, via presynaptic H_3 receptors, indirectly affects arousal mechanisms controlled by postsynaptic H_1 receptors.

The effects observed after blockade of cerebral H_1 receptors by various antagonists administered alone also support the idea that endogenous HA is critically involved in the control of wakefulness. Systemic administration of mepyramine, one of the most selective H_1 antagonists, in low dosage (1–5 mg/kg) causes a significant dose-dependent increase in slow-wave sleep at the expense of wakefulness and paradoxical sleep in rats (472), dogs (808, 809), and cats (437). A similar effect is also observed in rats treated with diphenhydramine (394). In humans, mepyramine was recently shown not to affect the number of awakenings during sleep or the total sleep time (498). However, there is an abundant literature showing that many H_1 antagonists administered to humans during the day produce marked drowsiness, increase the tendency to sleep, decrease the sleep latency, and impair various performances (188, 208, 497). These various properties are designated together under the name of sedative properties that most H_1 antagonists share. All these compounds have the ability to occupy cerebral H_1 receptors at low dosages, i.e., in the therapeutic range or below, as judged from the [3 H]mepyramine binding test in the living mouse (589, 591). In contrast a number of recently designed compounds, which do not easily occupy cerebral H_1 receptors, as indicated by either the *in vivo* [3 H]mepyramine binding test or the direct measurement of their cerebral level, do not share these sedative properties and are therefore increasingly used in the therapy of allergic diseases (195, 497, 589, 591). Interestingly a variety of psychotropic agents, currently used in therapeutics as either antipsychotics or antidepressants, which display strong affinity for H_1 receptors *in vitro* (3, 287, 288, 610, 611, 757) and occupy cerebral H_1 receptors when administered at low dosage (589, 591), do share these characteristic sedative properties. Starting from these various observations it was proposed that sedation elicited by these various drugs in humans could be ascribed to blockade of the arousal mechanisms mediated by histaminergic neurons in brain (589, 591, 611, 655, 662). It has been argued that sedation may as well be ascribed to other properties of these compounds, i.e., to their ability to

block muscarinic and α_1 -adrenergic receptors, or to their local anesthetic activity (334, 696, 753, 780). However, in most cases, the affinity of these drugs for these other targets is much lower than for H_1 receptors so that only the latter are likely to be occupied in brain at low therapeutic dosage: for instance the K_i of mepyramine for H_1 receptors is at least 1,000-fold lower than for muscarinic receptors (420). In addition, the high potency toward H_1 receptors is the sole common property of these various sedative compounds.

The critical role of histaminergic neurons in arousal mechanisms is not only supported by pharmacological studies but also by the observations that bilateral damage or experimental lesioning of the posterior hypothalamus is accompanied by a state of somnolence or hypersomnia in humans (791a), monkeys (597), rats (464, 488), and cats (484, 485, 727). Furthermore, lesions of the ventrolateral posterior hypothalamus induced in cats by the neurotoxin ibotenic acid specifically aimed at destroying HA perikarya were followed during the next days by large decreases in wakefulness at the benefit of paradoxical and then of slow-wave sleep; after 3 days the animals recovered their control level of sleep, suggesting the intervention of compensatory mechanisms (638).

Cortically projecting HA neurons of rat tuberomammillary nucleus share with other aminergic neurons believed to control states of sleep and wakefulness a number of electrophysiological properties evidenced by extracellular recordings (604). They are firing spontaneously, slowly (2.0 ± 1.5 Hz) and with a regular pattern; their action potentials are of long duration (2–6 ms), with a pattern suggesting the existence of an electrotonic delay between spontaneously generated initial segment and somatodendritic spikes; and corresponding axons display low conduction velocity (0.3–0.5 m/s) consistent with the ultrastructural observations that a large fractions of HA axons are unmyelinated.

Both neurochemical and electrophysiological studies indicate that the activity of histaminergic neurons is maximal during periods of wakefulness. In several rat and guinea pig brain areas, particularly the hypothalamus, the HA level shows a reliable circadian rhythm with the minimum in the dark phase, during which rodents are the more active (529, 660, 777, 793); although levels of His and HDC were not modified, synthesis of [3 H]HA in hypothalamic slices was significantly higher when rats were killed during the dark phase (660). Because decreased amine levels and increased synthesis rates are usually associated with enhanced neuronal activity, it was postulated that this was also the case for histaminergic neurons and that these observations were taken as supporting their role in arousal mechanisms (660).

In the freely moving cat, single-unit extracellular recordings in the ventrolateral posterior hypothalamus detected two populations of neurons, the activity of which was strictly related to cortical desynchronization (784). One of them, which displayed electrophysiological properties very similar to HA neurons recorded in the tuberomammillary nucleus of the anesthetized rat

(604), was highly selective for the waking state. During active waking these neurons discharged slowly and regularly, the firing rate then became progressively slowed during "calm waking" and, even more, light slow-wave sleep; these neurons were completely silent during deep slow-wave or paradoxical sleep (784). Barbiturates and other hypnotics dramatically decrease HA turnover in brain (327, 571).

Hence a variety of complementary experimental approaches indicate that HA neurons exert a major control in waking mechanisms, their best substantiated functional role so far. Available experimental evidence suggests that this action is mainly subserved via H_1 receptors, but the role of H_2 receptors remains to be thoroughly investigated. It has been underlined that the essentially modulatory mode of action of HA mediated by H_2 receptors at the cellular level and the anatomic disposition of HA pathways fit particularly well with a role in the regulation of states of awareness (276, 577). Finally, H_3 receptors may also participate by controlling not only the activity of HA neurons but also that of other neuronal systems.

XIII. ROLE OF HISTAMINERGIC NEURONS IN CONTROL OF VARIOUS BEHAVIORS

Relatively little research has been centered on the role of histaminergic systems in the control of complex behaviors (for review see Ref. 816).

A. Stress

Contradictory results have been reported regarding the effects of various stressful procedures in rats and mice.

In rats, forced immobilization and/or cold exposure decreased HA levels and increased HA turnover in hypothalamus (742, 744), but the effect on HA levels could not be confirmed by others (408). Air blasts increased HA levels and HDC activity in rats (461, 463).

In mice, forced immobilization for a relatively short period reduced whole brain HA turnover without affecting HA levels (789), whereas the same treatment for several hours decreased HA levels (745). Footshock stress for 30-120 min did not affect HA levels but enhanced HA turnover, an effect partly mediated by endogenous opioids (835).

B. Motor Activity

Intracerebroventricular administration of HA elicits biphasic changes in spontaneous locomotor activity in fowl (509), rats (373), and goats (774), with the hyperactivity response being, in all cases, mediated by H_1 receptors. However, in other studies only hypoactivity was observed (110, 525). Inhibition of locomotion, apparently mediated by H_1 and H_2 receptors, was observed in rats shortly after injection of HA into the ven-

tral hippocampus (14). Intra-accumbens injection of HA in rats elicited an initial hypoactivity, apparently mediated by H_3 receptors, followed by hyperactivity, apparently mediated by H_1 receptors (93, 94).

In mice, histidine loads reduce the amphetamine-induced locomotor activity (142, 355), an effect that might involve endogenous HA, as it is suppressed by administration of α -FMH (355).

In humans, several H_1 antagonists known to cross the blood-brain barrier impair psychomotor performance evaluated in a variety of complex skilled tasks (for review see Ref. 816).

C. Drinking and Eating

A role for peripheral HA in the control of peripran-dial drinking has been proposed (415) but is not considered here. When injected into several hypothalamic areas, particularly the medial rostral areas, HA elicits drinking in water-satiated rats and increases drinking in water-deprived rats (247, 430, 431). These effects appear to involve both H_1 and H_2 receptors, but blockade of these receptors by peripherally administered antagonists does not result in clear-cut effects on drinking behavior (415-417, 431).

When injected intracerebroventricularly, HA suppresses food intake in cats, an effect possibly mediated by H_1 receptors (133). However, in rats, when the amine is injected into the hypothalamus (136) or continuously infused into the suprachiasmatic nucleus (793), it has an opposite effect.

A possible role of endogenous HA in the control of food intake is suggested by the observation that H_1 but not H_2 antagonists induce feeding in rats when infused into the ventromedial hypothalamus during the light phase of the day; this effect was prevented by pretreatment with α -FMH (527a, 634, 635). Histidine loads (685) or thioperamide (T. K. Sakata, personal communication) suppress food intake.

D. Aggressive Behaviors

Intracerebroventricular administration of HA decreases electric shock-induced fighting in rats (450, 598) but has an opposite action when administered in high doses to mice (486). Histidine loads inhibit the same behavior in mice (142). Various H_1 antagonists, generally in high dosage, suppress isolation-induced fighting in mice (46) or muricide activity in rats (527).

E. Self-Stimulation, Reinforcement, and Aversion

Histamine injected into rat hypothalamic perifornical area, where an electrode for self-stimulation was implanted, inhibited self-stimulation, and the effect was blocked by H_1 antagonists (136). Mepyramine decreases self-stimulation, but chlorpheniramine has an opposite effect (807).

The H_1 antagonists are self-administered intravenously in squirrel monkeys (63) but not orally in rats (222).

When intracerebroventricular administration of HA was paired with administration of a sucrose solution, taste aversion to the later developed (596).

F. Learning

Intracerebroventricular administration of HA to rats improved the retention of a learned behavior, apparently via stimulation of both H_1 and H_2 receptors (161).

G. Discriminative Properties of H_1 Antagonists

In various animals trained to discriminate a H_1 antagonist from saline, there is complete generalization to most other drugs of this class (533, 815, 823). This suggests that the H_1 antagonists share some common behavioral properties but does not clarify the nature of the latter.

H. Hallucinatory Properties of H_2 Antagonists

There are several reports indicating that in a small number of patients taking cimetidine or ranitidine visual or auditory hallucinations may occur, perhaps as a result of altered blood-brain barrier permeability (for review see Ref. 816). It is not clear, however, whether these effects are selectively related to H_2 receptor blockade.

XIV. CONCLUSION

During the last few decades, many reviews on the physiological role of HA in the brain were almost uniformly concluded by the assertion that the amine should be considered as a putative neurotransmitter. The data reviewed here demonstrate, beyond any reasonable doubt, that this role is now fully established. Histaminergic neurons, although in small number, constitute one of these long tracts with widespread projections to large CNS areas, particularly in diencephalon and telencephalon. The localization of their target cells and the modes of action of HA at their level, as it is mediated by the three receptor subtypes, seems also largely, although incompletely, unraveled. From the available information it has been for a long time suspected that histaminergic neurons may coordinate diverse sensory, motor, hormonal, and vegetative functions to act in a concerted manner. These rather vague functions are similar to those currently ascribed to other aminergic neurons (noradrenergic, serotonergic), but the picture is somewhat less clear in the case of HA. One of the major challenges to take up now seems to be the understanding of the exact functional role of histaminergic neurons.

Their implication in a variety of biological and physiological processes (e.g., arousal, pituitary hormone secretion, control of cerebral circulation, thermoregulation) has been so far mainly suggested from the observed actions of HA or, in few cases, of agents modifying histaminergic transmissions in the brain. However, in most cases, one notable exception being arousal: there is a lack of evidence that these physiological activities are correlated with changes in neuronal histaminergic activity.

Monitoring these changes in behaving animals seems a prerequisite to more firmly confirm these various contentions. Establishing the nature of the information received by histaminergic neurons seems equally important in this respect. Also, as in the case of most other neuronal populations, the functional significance of coexisting neurotransmitters, which are particularly numerous in histaminergic neurons, needs to be established. In addition there is, so far, no clear indication regarding a possible implication of histaminergic neurons in pathophysiology.

Finally, a major challenge that remains to be taken up is the understanding of the functions of the nonneuronal store(s) of HA in the CNS.

The dramatic progress recorded during the last few years in understanding the other functions of the amine make us confident that little time will elapse before these remaining and exciting physiological problems are solved.

The skillful secretarial assistance of Annie Galtier and Mireille Cestrières is gratefully acknowledged.

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European Neuropsychopharmacology 14 (2004) 332–336

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The effect of famotidine addition on olanzapine-induced weight gain in first-episode schizophrenia patients: a double-blind placebo-controlled pilot study

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Received 2 May 2003; accepted 16 October 2003

Abstract

Olanzapine treatment is associated with substantial weight gain. In this double-blind placebo-controlled study we evaluated whether the H2 antagonist famotidine may prevent/attenuate olanzapine-induced weight gain. Fourteen first-episode DSM-IV schizophrenia patients were randomly allocated to receive either famotidine (40 mg/day, $n=7$) or placebo ($n=7$) in addition to olanzapine (10 mg/day) for 6 weeks. All patients completed the trial. Patients in both groups showed a similar increase in body weight (olanzapine/famotidine: 4.8 (3.2) kg and olanzapine/placebo: 4.9 (1.6) kg, respectively; a between-group difference of 0.14 (1.3) kg). Four of seven (57.1%) patients in the olanzapine/famotidine group and three of seven (42.9%) in the olanzapine/placebo group gained at least 7% of their initial body weight, a cut-off for clinically significant weight gain. Famotidine addition was safe and well tolerated and did not interfere with olanzapine's therapeutic effect. In conclusion, famotidine (40 mg/day for 6 weeks) is not effective in preventing/attenuating weight gain in olanzapine-treated first-episode schizophrenia patients.

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Keywords: Olanzapine; Histamine H2 antagonist; Weight gain; Famotidine; Schizophrenia

1. Introduction

Atypical antipsychotic agents, primarily olanzapine and clozapine, have been associated with significant weight gain (Allison et al., 1999). The mechanism underlying weight gain induced by atypical antipsychotics has not been clarified, though serotonergic, noradrenergic and histaminergic systems have been implicated (Baptista et al., 2002). Within the histaminergic system, the histamine H2 receptor appeared to be one of the possible mediators of feeding behavior and weight regulation (Doi et al., 1994). It was shown that H2 antagonists (cimetidine, ranitidine, famotidine) attenuated weight gain in rats (Stoa-Birketvedt et al., 1997), and cimet-

idine reduced weight in obese humans (Stoa-Birketvedt, 1993; Stoa-Birketvedt et al., 1998). Administration of the H2 antagonist nizatidine was associated with weight reduction in some olanzapine-treated schizophrenia patients (Sacchetti et al., 2000; Cavazzoni et al., 2003).

As part of our ongoing project aimed to evaluate the preventing/attenuating weight gain potential of pharmacological agents exerting selective effect at serotonergic, noradrenergic and histaminergic systems (Poyurovsky et al., 2002, 2003), we sought to determine whether famotidine may be effective in limiting weight gain in olanzapine-treated schizophrenia patients. Addition of famotidine to typical antipsychotics in schizophrenia patients had a beneficial adjunctive effect and was safe and well tolerated (Kaminsky et al., 1990; Rosse et al., 1996). To the best of our knowledge this is the first study evaluating the putative weight attenuating effect of famotidine in schizophrenia patients treated with the atypical antipsychotic olanzapine.

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Since young and previously untreated patients seem to be particularly vulnerable to olanzapine-induced weight gain (Kinon et al., 2000; Potenza et al., 1999), we evaluated the effect of famotidine on weight gain in first-episode schizophrenia patients.

2. Experimental procedures

2.1. Patient sample

The study sample consisted of 14 patients (nine men, five women) hospitalized for a first-episode of acute psychosis at the Tirat Carmel Mental Health Center, Tirat Carmel (Israel). All met DSM-IV criteria for schizophrenic or schizophreniform disorder. The diagnosis was based on the Structured Clinical Interview for DSM-IV Axis-I Disorders, Patient Edition (SCID-P) (First et al., 1995). Exclusion criteria were: major mood disorders, substance-induced psychoses, medical illnesses that could affect body weight (e.g. diabetes mellitus, hypothyroidism) and patients who had body mass index (BMI) >30 kg/m². None of the study participants had abnormal findings on routine physical examination and laboratory tests. The study was approved by the Institutional Review Board. Written informed consent was obtained from all participants after they received a full explanation of the nature of the study.

2.2. Study design

A double-blind placebo-controlled randomized design was used. The participants were randomly allocated to receive either famotidine (40 mg/day at 08:00 h; $n=7$) or placebo (at 08:00 h; $n=7$) in addition to olanzapine (10 mg at 20:00 h) for 6 weeks. Administration of trihexyphenidyl (5–10 mg/day) for extrapyramidal side effects (EPS) and diazepam (5–10 mg/day) for insomnia or agitation were allowed on an as-needed basis. The doses of all medications remained unchanged during the entire study period. Meals were served three times a day, and patients were not placed on a special diet or special physical exercise program for weight reduction.

2.3. Assessments

Weight and BMI were measured at baseline and at weeks 1, 2, 4 and 6 at 08:00 h before meals. All weight measurements were performed by a research nurse blinded to the patients' treatment assignment. Clinical assessment instruments included the Clinical Global Impression (CGI) scale for severity of psychosis (Guy, 1976), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983). Drug-induced EPS were evaluated by the Simpson–Angus Scale (SAS) (Simpson and Angus, 1970). Other emergent drug-induced side effects were

closely monitored. Clinical ratings were done at baseline and at the end of week 6 by the same trained psychiatrist (V.T.) who was blinded to the patients' treatment assignments.

2.4. Statistical analysis

Chi-square (χ^2) and Student's *t*-test were used as appropriate to evaluate between-group differences in baseline characteristics and changes of rating scale scores from baseline to endpoint. Between-group differences in body weight and BMI were analyzed using analysis of covariance with repeated measurements (ANCOVA-RM) with the baseline weight or BMI as covariates. The relationship between initial BMI and body weight changes at 6 weeks was assessed using Pearson's correlation. All tests were two-tailed; *P*-value less than 0.05 was considered significant. Results are presented as mean \pm S.D.

3. Results

Prior to the initiation of olanzapine treatment all participants were treated during the current first admission by typical antipsychotic agents [haloperidol 5–10 mg/day ($n=10$) or perphenazine 8–16 mg/day ($n=4$)] for less than 4 weeks. The olanzapine/famotidine group did not differ in any of the demographic, clinical or weight characteristics from the olanzapine/placebo group at baseline (Table 1). Body mass indices were within the normal range (18.5–24.9 kg/m²). All study patients completed the 6-week trial.

Patients in both groups revealed similar gradual increase in body weight and BMI (Table 2). ANCOVA-RM for weight and BMI found lack of significant group effect [weight: $F(1,11)=0.045$; $P=0.836$; BMI: $F(1,11)=0.059$; $P=0.81$]

Table 1
Baseline demographic, clinical and weight-related characteristics (mean \pm S.D.) of first-episode schizophrenia patients treated with olanzapine/famotidine ($n=7$) or olanzapine/placebo ($n=7$)

Patient variables	Olanzapine/famotidine	Olanzapine/placebo	Statistics
Demographics	23.1 (1.4)	22.1 (1.9)	$t=1.23$ $P=0.24$
Age (years)	4.3	5.2	$\chi^2=0.31$ $P=0.58$
Gender (M:F)	2.9 (3.2)	2.2 (1.9)	$t=0.50$ $P=0.63$
Duration of illness (years)	12.3 (5.0)	13.1 (3.2)	$t=0.36$ $P=0.73$
<i>Rating scale scores</i>			
SAPS	8.6 (3.7)	7.7 (3.3)	$t=0.48$ $P=0.64$
SANS	12.0 (4.2)	12.3 (5.0)	$t=0.12$ $P=0.91$
CGI	5.0 (1.0)	4.6 (0.5)	$t=0.95$ $P=0.36$
SAS	13.4 (2.1)	13.4 (2.1)	$t=0.93$ $P=0.37$
<i>Weight/BMI</i>			
Weight (kg)	67.2 (7.7)	64.7 (6.5)	$t=0.66$ $P=0.52$
BMI (kg/m ²)	22.3 (2.0)	23.1 (3.3)	$t=0.55$ $P=0.59$

SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; CGI, Clinical Global Impression; SAS, Simpson–Angus Scale; BMI, body mass index.

Table 2

Body weight and BMI (mean \pm S.D.) indices and changes from baseline in patients treated with olanzapine/famotidine ($n=7$) or olanzapine/placebo ($n=7$) for 6 weeks

	Olanzapine/famotidine				Olanzapine/placebo			
	Weight	Δ weight	BMI	Δ BMI	Weight	Δ weight	BMI	Δ BMI
Baseline	67.2 (7.7)		22.3 (2.0)		64.7 (6.5)		23.1 (3.3)	
Week 1	68.4 (8.6)	1.3 (1.3)	22.7 (2.3)	0.4 (0.4)	66.4 (5.5)	1.7 (1.7)	23.7 (3.1)	0.7 (0.3)
Week 2	69.1 (9.2)	2.0 (2.0)	22.9 (2.4)	0.6 (0.5)	67.1 (5.5)	2.4 (1.8)	23.9 (3.0)	0.9 (0.5)
Week 4	71.1 (9.9)	4.0 (2.8)	23.6 (2.5)	1.3 (0.7)	68.3 (5.8)	3.6 (1.1)	24.3 (3.1)	1.3 (0.3)
Week 6	72.0 (9.7)	4.8 (3.2)	23.9 (2.4)	1.6 (0.8)	69.6 (6.1)	4.9 (1.6)	24.8 (3.2)	1.7 (0.3)

Δ Weight and Δ BMI, difference from baseline.

The mean weight gain in the olanzapine–famotidine group was 4.8 (3.2) kg, and in the olanzapine–placebo group 4.9 (1.6) kg; a negligible difference of 0.14 (1.3) kg ($t=0.21$, $df=12$; $P=0.91$). Four of seven (57.1%) patients in the olanzapine/famotidine group and three of seven (42.9%) patients in the olanzapine/placebo group gained more than 7% of initial body weight, a cut-off for clinically significant weight gain ($\chi^2=0.29$; $df=1$, $P=0.59$). There was no correlation between baseline BMI and the increase in body weight at 6 weeks in either group (olanzapine/famotidine: $r=-0.03$, $df=6$, $P=0.91$; olanzapine/placebo: $r=0.12$, $df=6$, $P=0.72$).

There was a significant decrease in the CGI scores within each group from baseline to week 6 (olanzapine/famotidine 5.0(0.8) vs. 3.7(0.8), $t=3.04$, $P<0.01$; olanzapine/placebo 4.6(0.4) vs. 3.6(0.8), $t=2.96$, $P<0.01$), and non-significant decrease in SAPS (olanzapine/famotidine 8.6(3.7) vs. 5.9(3.1), $t=1.48$, $P=0.16$; olanzapine/placebo 7.7(3.3) vs. 6.0(4.4), $t=0.82$, $P=0.43$) and SANS scores (olanzapine/famotidine 12.3(3.0) vs. 9.4(3.3), $t=1.17$, $P=0.11$; olanzapine/placebo 13.1(2.9) vs. 11.3(2.5), $t=1.24$, $P=0.24$). No between-group differences were found in changes from baseline in either CGI ($t=0.77$, $P=0.46$), SAPS ($t=0.64$; $P=0.54$) or SANS ($t=0.41$, $P=0.69$) scores.

There was a significant improvement of Parkinsonian symptoms from baseline to endpoint as measured by SAS, in both groups (olanzapine/famotidine 13.4(1.3) vs. 8.9(1.6), $t=5.76$, $P<0.01$; olanzapine/placebo 15.9(4.4) vs. 10.9(1.9), $t=2.76$, $P=0.02$), with no revealed between-group difference ($t=0.16$, $P=0.88$). Four of seven (57.1%) patients in the olanzapine/famotidine group and five of seven (71.4%) in the olanzapine/placebo group reported daytime somnolence ($\chi^2=0.31$, $df=1$, $P=0.58$).

4. Discussion

The results of the present study indicate that administration of olanzapine with either famotidine or placebo is associated with substantial weight gain in first-episode schizophrenia patients. Roughly half of the study participants exhibited clinically significant weight gain. These findings are consistent with our previous report demonstrating a similar magnitude of weight increase in first-episode schizo-

phrenia patients treated with olanzapine and either fluoxetine or placebo (Poyurovsky et al., 2002). In addition, these findings substantiate earlier reports indicating that young and previously untreated schizophrenia patients are vulnerable to weight gain during the initial stages of olanzapine treatment (Kinson et al., 2000; Potenza et al., 1999).

The major finding of the present study is that the H2-antagonist famotidine (40 mg/day) co-administered with olanzapine was ineffective in attenuating weight gain in first-episode schizophrenia patients. Patients treated with the olanzapine/famotidine combination revealed an increase in body weight similar to their counterparts in the olanzapine/placebo group [4.8 (3.2) and 4.9 (1.6) kg, respectively], and no patients in either group maintained their initial weight. Noteworthy, similar to our previous reports (Poyurovsky et al., 2002, 2003) we found no significant correlation between initial BMI and change in body weight at the end of 6 weeks.

Although an initial report describing the potential of the H2-antagonist nizatidine (300 mg/day) to attenuate olanzapine-induced weight-gain was encouraging (Sacchetti et al., 2000), a subsequent controlled study demonstrated only an early transient effect of nizatidine (300 mg b.i.d.) in limiting olanzapine-induced weight gain that waned by week 16 of the trial (Cavazzoni et al., 2003). Overall, it seems that H2 antagonists (famotidine, nizatidine) are of limited value in prevention and/or attenuation of olanzapine-induced weight gain in schizophrenia patients.

In contrast to the positive effect of add-on famotidine on clinical ratings in chronic schizophrenia patients receiving typical antipsychotics (Rosse et al., 1996; Kaminsky et al., 1990), the addition of famotidine revealed no adjunctive clinical effect on both positive (SAPS) and negative (SANS) symptoms in our first-episode olanzapine-treated schizophrenia patients. The lack of effect of add-on famotidine on schizophrenia symptoms may be accounted for by the small sample size and short duration of treatment. Famotidine addition was safe and well tolerated by olanzapine-treated patients. No treatment-emergent EPS were reported. Moreover, olanzapine treatment with either famotidine or placebo was associated with a significant improvement of Parkinsonian symptoms induced by typical antipsychotics administered prior to olanzapine initiation.

The major limitations of the present study are small sample size, fixed doses of both famotidine and olanzapine

and short duration of trial. The absence of a significant between-group difference in weight gain may reflect a type II error. The slight attenuation of weight gain (0.14 kg) by famotidine might be a chance finding or a real effect, and the small sample size is insufficient to determine which is correct. According to power analysis with sample sizes, as in our study ($n=7$ in each group), we would have detected with a power of 80% only differences in means larger than 3.96 kg.

Several factors may account for famotidine's failure to attenuate olanzapine-induced weight gain. Olanzapine blood levels may be increased by add-on famotidine and thus counteract famotidine's putative weight reducing effect. However, this seems unlikely, since famotidine appears not to be metabolized by hepatic enzymes (Langtry et al., 1989) and no significant pharmacokinetic interactions between famotidine and antipsychotics have been reported (Prell et al., 1996). In addition, weight gain potential was reported not to correlate with olanzapine dose and/or blood levels (Kinon et al., 2000). It is also possible that higher famotidine doses may be required to affect both peripheral and central histaminergic mechanisms relevant to body weight regulation (Stoa-Birketvedt et al., 1997). Finally, there is increasing evidence that H1 rather than H2 antagonism may be pertinent to antipsychotic drug-induced weight gain. It was shown that H1-receptor antagonism increased feeding in rodents (Fukagawa et al., 1989), and H1-knockout mice are resistant to the anorectic effect of leptin and prone to obesity (Masaki et al., 2001). Recently, Kroeze et al. (2003) evaluated the relationship between receptor affinities profile of typical and atypical antipsychotics with their potential to induce weight gain and found that the most robust predictor of a drug's propensity to increase weight was its affinity for the H1-receptor. Noteworthy, antipsychotic agents (clozapine, olanzapine) and antidepressants (amitriptyline, mirtazapine) with the highest propensity to induce weight gain are potent H1-antagonists. Finally, other than histaminergic mechanisms (e.g. 5H2C, beta-adrenergic) are also involved in antipsychotic-induced weight gain (Baptista et al., 2002). Since weight gain appeared to be a risk factor for hyperlipidemia, diabetes mellitus and cardiovascular disease, a further search for effective pharmacological approaches for this common and potentially serious complication of antipsychotic drug treatment is warranted.

Acknowledgements

The authors acknowledge the assistance of Rena Kurs in preparation of the manuscript.

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Weight gain management in patients with schizophrenia during treatment with olanzapine in association with nizatidine

Manejo do ganho de peso em pacientes portadores de esquizofrenia durante o tratamento com olanzapina em associação com nizatidina

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Abstract

Objective: Weight gain is associated with treatment with many psychotropic agents. Nizatidine, H₂ receptor antagonist, has been proposed to have weight-reducing effects. This was a 12-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of nizatidine in reducing/limiting weight gain in patients with schizophrenia who have been under treatment with olanzapine. **Method:** Patients receiving olanzapine (2 to 6 months) and weight gain $\geq 5\%$ of their body weight during olanzapine treatment were randomly assigned to receive nizatidine 600 mg or placebo for up to 12 weeks. Change in psychopathology was assessed using Brief Psychiatric Rating Scale scores from baseline to endpoint. Safety was assessed using the Safety Assessed Software, assessment of glucose and lipid blood levels, and treatment-emergent adverse events. **Results:** Out of 54 patients enrolled in this analysis, 45 completed the protocol. The mean weight change prior randomization was 7.6 kg and 7.3 kg for those randomized to placebo and nizatidine, respectively ($p = 0.828$). Patients receiving placebo and nizatidine had a mean weight gain of 12.3% (0.7 kg) and 12% (1.1 kg) from baseline to endpoint, respectively ($p = 0.9$). Patients from both groups experienced a statistically significant decrease on the Brief Psychiatric Rating Scale mean score from baseline to endpoint. Treatment-emergent adverse events were reported by 18.5% and 25.9% on the placebo and nizatidine group, respectively. There were no statistically significant differences in glucose and lipid blood levels from baseline to endpoint and between groups. **Conclusions:** The concomitant use of olanzapine with nizatidine was not effective in controlling weight gain in patients who had previously gained weight during treatment with olanzapine when compared to placebo.

Descriptors: Schizophrenia; Antipsychotics agents; Weight gain; Clozapine; Nizatidine

Resumo

Objetivo: Ganho de peso está associado ao tratamento com inúmeros psicotrópicos. O uso de nizatidina, um antagonista H₂, pode estar associado à redução de peso. Este foi um ensaio clínico aleatorizado, duplo-cego, controlado com placebo, de 12 semanas, desenhado para avaliar a eficácia da nizatidina em reduzir/limitar o ganho de peso em pacientes com esquizofrenia recebendo olanzapina. **Método:** Pacientes recebendo olanzapina (entre dois e seis meses) e com ganho de peso $\geq 5\%$ desde o início do tratamento foram aleatorizados para receber nizatidina 600 mg ou placebo. Alterações psicopatológicas foram avaliadas usando-se a Brief Psychiatric Rating Scale total. A segurança foi avaliada por meio da pontuação na Safety Assessed Software, avaliação dos valores de glicemia e lipídios e a incidência de eventos adversos decorrentes do tratamento. **Resultados:** Dos 54 pacientes incluídos na análise, 45 completaram o protocolo. A alteração média de peso antes da aleatorização foi de 7,6 kg e 7,3 kg nos pacientes aleatorizados para placebo e nizatidina, respectivamente ($p = 0,828$). Pacientes recebendo placebo e nizatidina tiveram, respectivamente, ganho médio de peso de 12,3% (7 kg) e 12% (1,1 kg) ao longo do estudo ($p = 0,9$). Ambos os grupos apresentaram diminuição estatisticamente significativa na pontuação média da Brief Psychiatric Rating Scale. Eventos adversos emergentes do tratamento foram relatados por 18,5% e 25,9% dos pacientes recebendo placebo e nizatidina, respectivamente. Não houve diferença estatisticamente significativa nos níveis glicêmicos e lipídicos do início ao final do estudo ou entre os grupos de tratamento. **Conclusões:** Comparado ao placebo, o uso concomitante de olanzapina e nizatidina não foi eficaz em controlar o peso em pacientes com ganho prévio de peso durante o tratamento com olanzapina.

Descritores: Esquizofrenia; Agentes antipsicóticos; Ganho de peso; Clozapina; Nizatidina

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Financing: This clinical trial was sponsored by Eli Lilly do Brasil Ltda
Conflict of interests: Dr. Sheila Seleri Marques Assunção worked for the company by the time the study was being conducted.
Maurício Silva de Lima and Oswaldo Bracco are Lilly employees.
Submitted: September 5, 2005
Accepted: July 21, 2006

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Introduction

According to the mental health supplement of the National Health Interview Survey,¹ body mass index (BMI) distribution of schizophrenic individuals is generally similar to or higher than that of the general population, and weight changes in schizophrenic patients were well documented even in the pre-antipsychotic drug era.² The reported prevalence of overweight and obesity in patients with schizophrenia has been found to range from 40% to 62%,³⁻⁷ and obesity is a complicating factor in many medical illnesses commonly seen in patients with schizophrenia.⁸⁻⁹ Atypical antipsychotics are associated with superior tolerability, compliance, and relapse prevention and have led to improved treatment for patients with serious mental illness.¹⁰ However, novel antipsychotics apparently produce an even greater weight gain when compared to typical agents.¹¹⁻¹³ A recent meta-analysis of over 80 studies on weight change during antipsychotic treatment showed a mean weight gain after 10 weeks of treatment of 9.8 lb (4.45 kg) with clozapine, 9.1 lb (4.15 kg) with olanzapine, and 4.6 lb (2.10 kg) with risperidone compared to 2.4 lb (1.08 kg) with the typical antipsychotic haloperidol.¹¹ Many theories (including increased food intake¹⁴⁻¹⁵ have been advanced to explain the antipsychotic-related weight gain in schizophrenia.¹⁶⁻¹⁷ Recently, serotonin, dopamine, and histamine receptor blockade has been implicated.¹⁸⁻¹⁹ In this manuscript, it is of particular interest the role of histamine in the regulation of appetite and satiety as it is well known that atypical antipsychotics have a much greater affinity to the H-1 receptor when compared to typical medications.²⁰ This fact is consistent with the hypothesis that effects on histamine may contribute to atypical antipsychotic-treatment associated weight gain. Cimetidine, an H-2 receptor antagonist, has been reported to reduce weight in overweighted healthy subjects,²¹ and also in overweighted type 2 diabetes mellitus patients,²² although this finding has not been unequivocal.²³⁻²⁴ Gastrointestinal regulatory peptides, such as cholecystokinin, have been proposed to mediate the satiety signal from gut to brain. In normal subjects, cimetidine increased the basal cholecystokinin and may be one mechanism by which it reduces the appetite. A report by Sacchetti et al. described a patient with repeated episodes of weight gain during olanzapine treatment who experienced weight reduction after 4 to 5 weeks of therapy with nizatidine (150 mg BID), an H-2 antagonist.²⁵ In a 16-week double-blind trial, Cavazzoni et al. reported significantly less weight gain at weeks 3 and 4 with olanzapine+nizatidine 300 mg BID compared to olanzapine+placebo, although no statistical difference between groups was seen at 16 weeks.²⁶ In that study, nizatidine was well-tolerated and did not adversely affect clinical outcomes. In an open-label study, Lopez-Mato et al. described that ranitidine also prevented or corrected weight gain in patients receiving olanzapine.²⁷

The studies by Cavazzoni et al. and Lopez-Mato et al. showed that H2 antagonists may prevent or reduce weight gain when initiated concomitantly with olanzapine treatment.²⁶⁻²⁷ During the treatment with olanzapine, approximately 25% of schizophrenic patients has a decrease in body weight or gain no weight.²⁸ In those individuals, a pharmacological approach to control weight gain is certainly not recommended. According to a review by Kinon et al., approximately 48% of olanzapine-treated patients gain less than 7%.²⁸ For these patients, behavioral and dietary changes may suffice to manage their body weight changes and no pharmacological approaches would be necessary.²⁸

The purpose of the present study was to evaluate whether the use of an H2 antagonist in schizophrenic patients who have already gained weight could promote stabilization or reduction in body weight. Additionally, patients were considered responders if remained in therapy for 6 weeks or more and had no weight gain or a weight gain $\leq 3\%$ since started using nizatidine (baseline). Non-responders were defined as any patients who failed to remain at least 6 weeks in the study and had gained $> 3\%$ since starting treatment with nizatidine. Possible effects of nizatidine on psychopathology and safety parameters were also assessed.

Method

1. Sample

Outpatient subjects (male or female, 18 to 65 years of age) met DSM-IV²⁹ diagnostic criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder. After a complete description of the study to the subjects, written informed consent was obtained. In order to be eligible to participate in this protocol, patients had to be in treatment with olanzapine (5 to 20 mg/day) for no less than 2 months and no more than 6 months, had a record of their body weight when initiated on olanzapine, had gained $\geq 5\%$ since initiated the treatment with olanzapine, and had a total BPRS score < 45 . Patients were excluded if they had any known physical illness that could affect body weight and composition, were currently participating in a formal weight loss program, or had a body mass index (BMI) ≥ 40 kg/m² or weight ≥ 114 kg. Patients with a diagnosis of diabetes mellitus could be enrolled provided their condition was under control and if they were in treatment for DM for at least 6 months. The study protocol was approved by Hospital Mario Kröeff Ethical Review Board on the 28th November 2002.

2. Study design

This was a randomized, double-blind, 12-week placebo-controlled trial. After a complete description of the study to the subjects, written informed consent was obtained. After baseline assessments, all eligible patients were randomized to receive placebo (PBO) or 300 mg nizatidine BID (NIZ). This study had a total of 4 follow-up interviews and assessments were performed in a monthly basis. Figure 1 shows the study design.

3. Assessments

Patients were weighed at each visit. All investigators were given detailed instruction at study start-up on uniform and consistent weight measurements. Psychopathology was assessed using the total score of the 18-item Brief Psychiatric Rating Scale (BPRS; each item rated from 1 to 7).³⁰ Safety parameters were assessed by treatment-emergent adverse events, routine laboratory analytes, and extrapyramidal symptoms (EPS), measured by the total score of the Simpson-Angus Scale.³¹ Treatment-emergent adverse events were considered those that worsened or were described for the first time after initiating the treatment with nizatidine.

4. Statistical analysis

A mixed-effects model for repeated measures analysis of variance (ANOVA) was used to analyze the primary outcome measure (i.e. mean changes in total body weight from baseline to endpoint) and other continuous data. When the distribution was not normal, it was used the Mann-Whitney non-parametric test. For the comparison between responders and non-

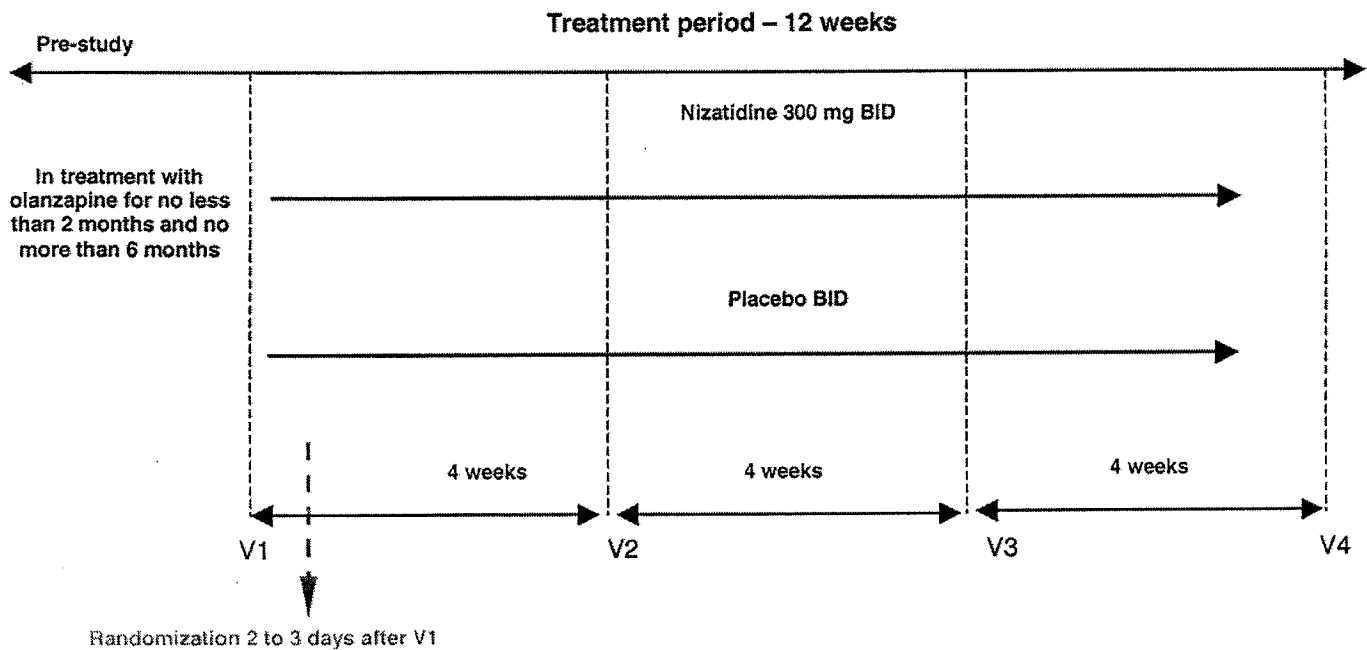


Figure 1 - Study design

responders, it was used the chi-square test. Results are expressed as the mean \pm standard deviation (SD), unless otherwise stated. Statistical significance was set at $p \leq 5$.

Results

1. Sociodemographic and clinical characteristics

A total of 54 patients were included in this analysis; 27 patients were randomized to receive nizatidine 300 mg BID and 27 to receive placebo, in association with their usual treatment with olanzapine (5-20 mg/day). Forty-five patients completed the treatment with no statistical difference between completers in both groups ($p = 0.39$). Age at first episode, number of previous episodes and hospitalizations during the last 6 months were assessed and groups were comparable regarding those clinical characteristics at baseline (Table 1). Additionally, the groups did not differ in terms of socio-demographic characteristics (Table 1). Out of the total sample, 59.3% ($n = 32$) were male and the mean age was 35.2 (SD \pm 12.2).

Patients had to have an increase of at least 5% in their body weight from the time they initiated on olanzapine and were

randomized. There was no statistical difference in the mean percentage of weight gain before randomization to PBO or NIZ (PBO = 12.3%, NIZ = 12%) ($p = 0.829$). Table 2 shows body weight mean values before and during the study. The mean duration on olanzapine treatment, before being randomized to nizatidine or placebo, was 2.9 months for both groups. Among the 54 patients included in the analysis, none had a previous diagnosis of diabetes and none developed DM during the 12-week period of the study.

There were no statistical or clinical significant differences between genders. From the baseline assessment females had a 12.5% increase in body weight after the beginning of olanzapine treatment and males 11.9%, with BMC of 26.0 and 26.3 for females and males, respectively.

2. Effect on weight

Both groups did not significantly differ with respect to amount of weight gain at endpoint: patients receiving NIZ had a mean weight gain of 1.1 kg and those randomized to PBO gained 0.7 kg ($p = 0.9$). Figure 2 shows the change in body weight between groups. Multiples comparisons along treatment visits,

Table 1 - Sociodemographic and clinical characteristics at baseline for both treatment groups

		Placebo	Nizatidine	Total	P-value
Mean age (SD) - years		34.9 (12.2)	35.5 (12.4)	35.2 (12.2)	0.45
Gender (n/%)	Female	13 (48.1%)	9 (33.3%)	22 (40.7%)	0.27
	Male	14 (51.9%)	18 (66.7%)	32 (59.3%)	
Ethnicity (n/%)	White	16 (59.3%)	20 (74.1%)	36 (66.7%)	0.45
	Black/ mulatto	9 (33.3%)	5 (18.5%)	14 (25.9%)	
	Other	2 (7.4%)	2 (7.4%)	4 (7.4%)	
Body weight when initiating treatment with olanzapine (kg; SD)		64.3 (12.2)	64.8 kg (13.4)	64.5 (12.7)	0.76
Mean time between time initiating on OLZ and baseline (months)		2.9 (1.1)	2.9 (1.2)	2.9 (1.1)	0.67
Age at first episode (years; SD)		24.9 (8.4)	22.3 (6.4)	23.6 (7.5)	0.21
Mean number of previous episodes (SD)		4.7 (5.0)	3.2 (4.3)	4.0 (4.7)	0.12
Hospitalization during the last 6 months	Yes	15 (55.6%)	9 (33.3%)	24 (44.4%)	0.23
	No	12 (44.4%)	18 (66.7%)	30 (55.6%)	

Table 2 - Body weight measures at different points during the treatment with olanzapine

	Mean body weight when initiating treatment with olanzapine	Mean weight change between initiating treatment with olanzapine and visit 1	Mean weight change in patients with ≤ 2 months of treatment with olanzapine and visit 1	Mean weight change in patients with > 2 months of treatment with olanzapine and visit 1	% of weight change since initiating treatment with olanzapine and visit 1
PBO	64.8 kg (SD ± 13.4)	7.6kg (SD ± 3.7)	6.5 (SD ± 3.5)	8.7 (SD ± 3.8)	12.3% (SD $\pm 6.9\%$)
NIZ	64.3kg (SD ± 12.2)	7.3 kg (SD ± 4.0)	6.8 (SD ± 3.8)	7.8 (SD ± 4.2)	12% (SD $\pm 7.5\%$)
p-value NIZ vs. PBO	0.76	0.828	0.76	0.76	0.829

regardless of treatment groups, showed that body weight at endpoint was statistically, although not clinically ($< 5\%$), higher when compared to baseline (V1 versus V4: $p = 0.002$); however, body weight at endpoint was significantly lower when compared to those at Visits 2 and 3 (V2 versus V4: $p = 0.003$, and V3 versus V4: $p = 0.001$).

3. Responders and non-responders

53.8% ($n = 28$) were considered responders, i.e., remained in therapy for at least 6 weeks and had no weight gain or had weight gain $\leq 3\%$ since started using nizatidine (baseline). There was no statistical difference in the rates of responders for nizatidine 57.7% and placebo 50% ($p = 0.58$). Females had a lower responder rate (39.3%), when compared to males (60.7%), but this difference was not statistically significant ($p = 0.63$).

4. Effect on psychopathology and safety

Significant improvement on the BPRS total scores was observed in both treatment groups from baseline to endpoint ($p < 0.001$ for both groups). However, the BPRS score was not significantly different between groups at endpoint (PBO: 23.7 ± 9.9 ; NIZ: 24.2 ± 8.5 ; $p = 0.12$). Figure 3 shows the changes in BPRS total score from baseline to endpoint in both groups. Decreases in BPRS total score were seen as early as week 4 (V1- NIZ: 27.5; PBO: 23.9 vs. V2 - NIZ: 25.4; PBO: 21.8; $p = 0.006$).

All patients showed a statistically significant improvement on the Simpson-Angus Scale from baseline to endpoint ($p < 0.001$). There were no statistically significant differences between groups at endpoint (PBO: 1.4 ± 2.8 ; NIZ: 0.6 ± 1.3 ; $p = 0.51$). There were no significant differences in treatment-emergent adverse events reported between groups (NIZ: 25.9% versus PBO: 18.5%; $p = 0.5$), and only 3 patients (1 NIZ; 2 PBO) discontinued the study due to an adverse event. Headache, somnolence, and hypersomnia were the only treatment-emergent adverse events reported by more than 2 patients. There were no significant differences between groups on any of the measured laboratory analyses (Table 3).

Discussion

The appropriate selection of APs ought to be based on drug efficacy and risk factors in clinical daily practice. Although more efficacious in a number of clinical outcomes, treatment with atypical antipsychotics may be associated with weight gain.¹¹⁻¹³ Thus, patients should be informed of that adverse event in order to avoid excessive weight gain. Nutritional advice must be given and regular physical exercise recommended. Many studies have shown that behavioral, pharmacological or a combination of both methods turned out to be efficacious in preventing weight gain.^{13,26,32}

At present, there is no standardized pharmacological treatment for antipsychotic-related body weight gain. Some studies have assessed the effects of agents such as amantadine, orlistat,

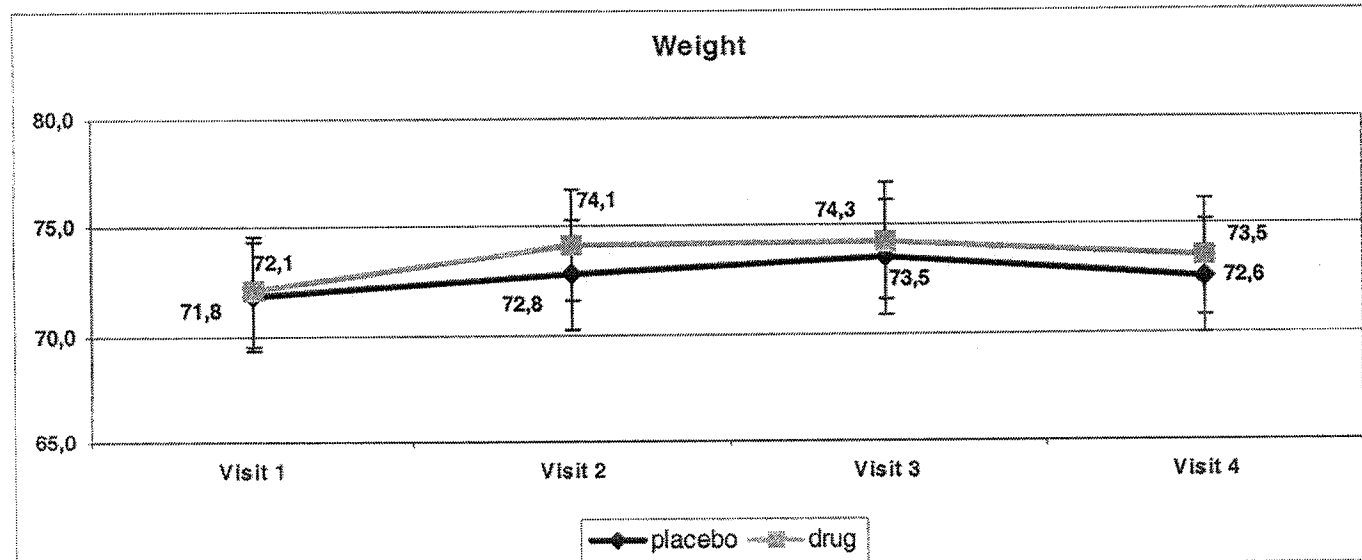


Figure 2 - Body weight changes from baseline to endpoint in patients receiving nizatidine or placebo

Table 3 - Laboratory analytes between treatment groups and from baseline to endpoint

	V1 (week 0)	V4 (week 12)	p-value NIZ vs. PBO	p-value V1 vs. V4
Glicemia			0.414	0.606
PBO	83.3 (10.2)	84.6 (14.7)		
NIZ	85.4 (12.0)	87.1 (14.5)		
Cholesterol total			0.241	0.630
PBO	191.3 (36.8)	180.3 (34.1)		
NIZ	195.5 (47.0)	198.8 (46)		
HDL			0.8	0.9
PBO	49.2 (9.4)	46.5 (12.7)		
NIZ	48.7 (13.4)	45.8 (10.6)		
LDL			0.34	0.77
PBO	191.3 (36.8)	180.3 (34.1)		
NIZ	195.5 (47.0)	198.8 (46.0)		
Triglycerides			0.38	0.28
PBO	148.2 (71.0)	152.7 (75.1)		
NIZ	168.4 (120.0)	179.4 (112.7)		

metformin, nizatidine, and topiramate as pharmacological alternatives to manage this adverse event.^{26,33-37} Treating weight gain with pharmacological agents in psychiatric patients must be done with caution as some drugs used to this purpose may exacerbate the psychiatric condition, once their primary site of action is the central nervous system.¹² Thus, the use of a medication to manage weight gain in psychiatric patients without central activity would be of particular interest.¹²

Previous studies showed that H2 antagonists might be related to weight loss in humans.^{21-22,25-27} Causing weight loss by a mechanism that is yet to be defined, H2 antagonists are more likely to have their the primary site of action outside the central nervous system, as H-2 antagonists as a class are very hydrophilic and cross the blood-brain barrier to a limited extent.³⁸ Due to their peripheral site of action, H2 antagonists were used in some studies to manage weight gain in schizophrenic patients on olanzapine. Among those studies two are of most interest due to their design and methodology.²⁶⁻²⁷

Cavazzoni et al. compared two different doses of nizatidine (300 mg QD and 300 mg BID) with placebo to manage weight gain in patients initiating treatment with olanzapine.²⁶ At weeks 3 and 4, patients treated with nizatidine 300 mg BID reported significantly less weight gain compared to placebo; however, no significant difference between the treatment groups was

seen at 16 weeks. The authors suggested that nizatidine 300 mg BID may have a potential effect, albeit transient and possibly dose-related. The authors hypothesized a rebound phenomenon of weight recovery, a decrease in compliance over time, and interindividual variability as possible reasons for the apparent lack of persistent effect of nizatidine in controlling weight gain.

Lopez-Mato et al. evaluated the efficacy of different doses of ranitidine in preventing or reducing weight gain in schizophrenic patients treated with olanzapine in an open-label trial.²⁷ According to their results, the use of ranitidine prevented or corrected weight gain in 59.6% of the patients receiving olanzapine. Patients not receiving ranitidine exhibited an average weight gain of 3.4 kilograms (SD: -2.5 to +16 kg), and an increase of 1.19 kg/m² in their BMI. Patients treated with ranitidine 300 mg/day gained 0.9 kilogram (SD: -4 and +10.6 kg), with an increase of 0.34 kg/m² in their BMI. For patients on the highest dose of ranitidine (600 mg), the weight gain curve trended towards normalization. They lost 1.6 kilogram and 0.6 points in their BMI, in average. Additionally, they lost up to -15 kilograms and gained less weight (up to 7 kilograms) when compared to those receiving a lower dose of ranitidine or placebo. Contrary to the study of nizatidine by Cavazzoni et al. the effect of weight control with ranitidine was sustained along all the study period.²⁶

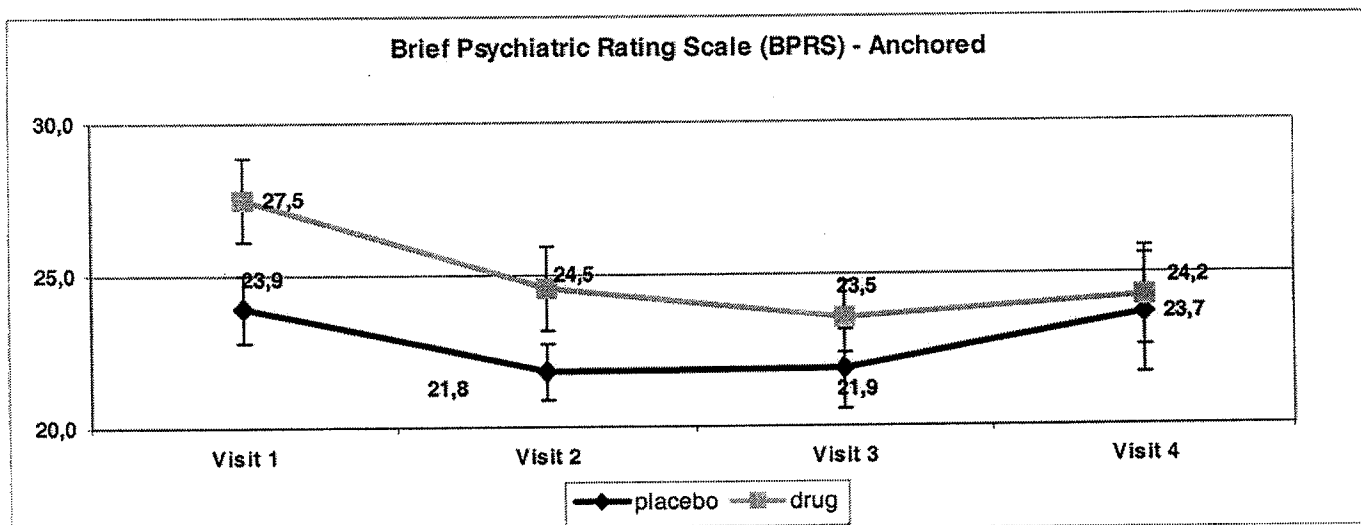


Figure 3 - Changes in BPRS total score from baseline to endpoint according to treatment groups

Our study had the main objective of assessing whether an H2 antagonist, nizatidine, could be of help for patients with schizophrenia or related disorders that had already had substantial weight gain ($\geq 5\%$) with olanzapine. If so, it would avoid unnecessary use of this pharmacological strategy to a significant part of patients who, during the course of their treatment with olanzapine, did not present weight gain nor had a weight gain that could be managed by behavioral and/or dietary strategies.²⁸

We demonstrated that nizatidine when administered to olanzapine-treated patients with previous weight gain did not differ from placebo in the amount of weight control. It could be hypothesized that the greater increases in body weight occurred most likely during the first months after initiating treatment with olanzapine (pre-study). Patients randomized to nizatidine gained on average 6.8 kg and those randomized to placebo, 6.5 kg, during that study period. Although continuing gaining weight, this increase was substantially lower (NIZ: 1.1kg and PBO: 0.7 kg) when compared to the initial phase of treatment with olanzapine. Those results are in accordance with previously published data, showing that the rate of weight gain appears to be more intense during the first 12 weeks of olanzapine treatment, occurring less rapidly in subsequent weeks, and plateauing around the 39th week.²⁸ That might be one explanation why nizatidine did not differ from placebo in controlling weight as most patients could already be in or close to the plateau phase.

Another concern related to the use of atypical antipsychotics is the potentially increased risk of treatment-emergent diabetes. Contrary to weight gain, that has been reported with some atypicals more than others (e.g., clozapine, olanzapine), recent reviews show that the potentially increased risk of DM appears to be a class-wide occurrence among the new generation antipsychotics.^{13,39} In our study, blood glucose and lipids levels did not differ from baseline to endpoint and between patients in the two treatment groups during the 12 weeks of the study duration.

There are consistent data suggesting that the main driver when choosing an antipsychotic treatment must be the drug efficacy.^{13,39} Although treated as a homogeneous group, effectiveness is different from one drug to another. For instance, in a recent meta-analysis, Davis et al. described that only clozapine, amisulpride, risperidone, and olanzapine were more efficacious than typicals, while other atypicals were not. After considering the drug's efficacy, medication's risk profile must also be considered.¹⁰

According to measures in the levels of psychopathology, extrapyramidal symptoms, laboratory analytes, and reports of treatment-emergent adverse events assessed during the study, nizatidine did not interfere with the efficacy and/or safety of olanzapine. This study did not have the intention to determine the efficacy or safety of olanzapine. Patients' levels of psychopathology were followed-up in the trial by using BPRS. Patients included in this study were not in an acute phase due to the inclusion criterion of a score on the total BPRS < 20 . Despite this low score at baseline, it is interesting to note that patients using olanzapine continued to show a slight, yet statistically significant, decrease in their level of psychopathology during the 12 weeks of the study duration. Furthermore, extrapyramidal symptoms also decreased in intensity, according to score at Simpson-Angus Scale.

1. Study limitations

This study has some limitations that must be considered. It could be argued that this sample size is not large enough

to detect differences between treatment groups. However, this may not be the main reason for these negative findings. There is some limitation in the design of the study. Before entering the study, patients were receiving olanzapine according to their physicians' discretion, as they were not in a controlled trial. Thus, the exact doses and compliance to the antipsychotic treatment might have substantially diverged among patients. Furthermore, patients in this study gained on average 7 kg after starting taking Olanzapine and before entering the trial. One could hypothesize that if nizatidine was delivered earlier before weight gain, during the first weeks of treatment, results might have favored this intervention.

Finally, only body weight at the time olanzapine was initiated was a required measure to be enrolled in this study, yet no requirement was made regarding metabolic parameters. Any conclusion about changes in those analyses must be taken very cautiously. The same caution must be observed regarding conclusions on psychopathology and extrapyramidal symptoms, as the study was not designed for purposes of efficacy and/or safety.

Conclusions

Our results showed that, when patients had already gained substantial weight with olanzapine treatment, the concomitant use of nizatidine did not differ from placebo in controlling weight gain. Olanzapine shows a remarkable efficacy in improving psychopathology in schizophrenic patients; however, some patients may experience significant weight gain. Innumerable studies show that weight gain can be adequately and successfully managed with behavioral and/or pharmacological approaches. The relatively rapid onset of weight gain with olanzapine suggests the importance of early intervention for weight gain mitigation. Proactive interventions to deal with this adverse event, regardless of the nature of the intervention, may result in weight stabilization/loss. Furthermore, appropriate attention to this issue can improve the quality of life for patients treated with antipsychotic drugs, and decrease morbidity and mortality due to weight-related disorders.

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